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LESIONS PRODUCED BY ARSENICALS AND THEIR BEARING ON THE PROBLEM OF SPECIFIC ARSENIC THERAPY.*

By Wade H. Brown, M. D.

(From the Laboratories of the Rockefeller Institute for Medical Research.)

The use of arsenic in the treatment of trypanosomiasis is now of some fifty years' standing. The first therapeutic experiments of this nature were those of Livingstone in the treatment of "fly bite" or nagana during his African explorations in 1858. True, he had no knowledge of the causative agent against which his therapy was directed and it was not until many years later, when the trypanosermal nature of nagana, surra, sleeping sickness, and other diseases of a similar character had been established, that the significance of these early therapeutic efforts was grasped and definite progress towards a rational therapy of these diseases was made.

Experimental arsenic therapy had its beginning in the demonstration by Lavéran and Mesnil of the trypanocidal action of arsenic in laboratory animals. This work, published in 1902, inspired a search for specific therapeutic agents and many other lines of therapy began to be developed in consequence—notably dye therapy, and later the use of compounds of antimony. The greatest achievement, however, came from the work of Thomas on atoxyl published in 1905, followed by that of Uhlenhuth extending the field of specific arsenic therapy to spirochætal infections. With the determination of the chemical constitution of atoxyl by Bertheim and Ehrlich, the foundations for the future development of specific arsenic therapy were completed. Under the leadership of Ehrlich, the achievements in this field of therapy during the last decade have indeed been most remarkable. But the end is not yet and there are many workers striving, with hope, to improve upon the results thus far obtained.

During the past several years, a small group of workers at the Rockefeller Institute, consisting of Drs. Jacobs and Heidelberger in the chemical department, and Dr. Louise Pearce and myself, have been struggling with the problem of specific chemotherapy. There are many phases of this work about which one might speak, but we have chosen that phase about which least has been said and which to our minds, at any rate, presents at once the most difficult and the most hopeful point of attack, namely, injury and its elimination.

Since the aim of all efforts to construct chemical compounds possessing specific action against agents of infection is not only to cure, but to cure with a minimum of risk and injury to the host, it is quite obvious that the attention of the experimental worker must be constantly centered upon two points—effect

*Read before The Johns Hopkins Hospital Medical Society, May 3, 1915.

upon the host and effect upon the parasite. These two phases of drug action are our directing forces and are of equal importance. Further, they are the criteria by which we must gauge the value of each product. Intensification of the action upon the parasite and the elimination of injury to the host become, therefore, our constant aim, and I refer here in particular to that phase of injury which gains expression in the form of organic lesions. While innumerable compounds of arsenic must have been investigated from this dual aspect, it is unfortunate that so little of the details of their action upon the animal organism has found a place in the literature. True, the pathology of arsenic poisoning has been most carefully worked out and serves as a valuable guide and standard for comparison but, apart from this, as I shall attempt to show, this knowledge avails but little in the problem of chemotherapy.

With the small group of compounds that we have studied thus far—about sixty in all—it has been our plan to determine not only their toxic limits, but the essentials of their pathological action in mice, rats, guinea-pigs, rabbits, and, in some instances, dogs. The toxicity of compounds with approximately the same percentage of arsenic has varied very widely, but not more so than the variety and severity of the tissue injury they are capable of producing.

Omitting most of the well-known lesions of arsenic, some conception of the complexity of the problem presented to the experimental worker may be conveyed by a brief description of the more important types of lesions produced in a given organ by different compounds of arsenic, the preferential action exhibited by different compounds for different organs, variations of the action in different animal species, and some of the so-called accidents. From these it will not be difficult to grasp the fundamental importance of the lesions of arsenicals to the experimental worker and perhaps also to the clinician.

The pathological changes that one encounters in the heart and blood-vessels constitute a group that are of great importance. Many of these lesions are extremely difficult of demonstration either to the naked eye or with the microscope; some are of the character of degenerative processes in the heart or vessel walls, which in themselves may seem of little importance but furnish a basis for more serious lesions, such as hemorrhage or thrombosis. With some compounds, subendocardial hemorrhages, myocardial hemorrhages, and hemorrhage into the substances of valves, have been practically constant. These lesions are especially striking in the heart of the dog, to which relatively large doses of atoxyl have been administered. They are also known to be produced by such substances as salvarsan and its various modifications.

Vascular occlusion is probably far more common as the result of poisoning with arsenic or compounds of arsenic than is generally recognized. These occlusions may be produced by either thrombi, formation of which is favored by vascular injury, or by emboli resulting from coagulation of blood elements. The seriousness of the injury produced by such vascular occlusions, of course, depends largely upon their extent and location, and all such changes may be regarded, therefore, as accidents. Many of them may be relatively harmless, whereas others, by chance involving tissue of vital importance, may lead to most serious consequences.

Turning now to the lungs, until recently we had observed no lesions of the lungs that could be regarded as both constant and characteristic of the action of any particular compound. We have, however, observed with at least five recent compounds, a characteristic type of lung injury. This injury consists of petechial hemorrhages, finely and uniformly distributed through the substances of a lung which is voluminous and pale. With some of these compounds, a lesion of identically the same character is present in the surface of the kidney, while with others the kidney lesion is slight or entirely absent. With at least two of these compounds, reduction of the dose leads to a disappearance of the lesions in the kidney and the lesions in the lungs persist as the one characteristic change produced by the compound.

The lesions of the liver have long ranked among the most important of the organic changes produced by arsenicals. For convenience, we may divide the lesions of this organ into three groups: first, the lesions of a diffuse character, showing no preference for any particular region or structure of the organ; secondly, those lesions produced by compounds manifesting preference for the central zone of the liver lobule, and thirdly, the lesions produced by compounds acting by preference upon portal structures and the peripheral zone of the lobule.

The lesions in the first group are, for the most part, degenerative in character and closely resemble the well-known changes produced by inorganic compounds of arsenic. To these, however, must be added instances of diffuse necrosis, in which the maximal action of the compound upon the liver manifests itself in a widely distributed necrosis of individual liver cells; finally, we may place here also the group of focal necroses which are quite frequent and characteristic of the action of many compounds of arsenic.

Lesions of the central zone also include degenerative processes and necroses. Fatty degeneration of the central zone of the liver lobule is quite frequent, and in some instances the most constant and striking lesion produced by certain compounds. In other instances, fatty degeneration gives place to necrosis and most of these central necroses differ in no wise from the central zone necrosis produced by a large number of chemical agents.

We have, however, one compound on our list that produces a series of lesions entirely different from any lesion-complex with which we are familiar. The action of this compound is characterized by the fact that lethal doses in the guinea-pig lead to profuse hemorrhage into the bile-ducts from which the animal may actually bleed to death. At autopsy the appearances presented are those of a nutmeg or extremely pale and pasty liver with a gall-bladder enormously distended with blood, while the kidneys are extremely pale throughout and the urinary bladder is distended with an almost water-clear urine. We have not found this lesion-complex so constant for any other animal. It has been observed but once in the rabbit, and we have failed entirely to produce it in the

dog, which may be explained by the fact that the dog occupies an anomalous position with reference to this compound, in that dogs tolerate more than twice as much of this particular arsenical than any other animal upon which we have tested it. This is, so far as we know, the only instance in which the dog tolerates more of an arsenical than other experimental animals. It is also of considerable interest that this particular compound is one very closely related to atoxyl, a substance to which the dog manifests an extreme degree of susceptibility, tolerating only 10 mg. per kilo of body weight, as against 170 mg. for the mouse or rat.

The repair that follows this type of central necrosis in the guinea-pig is also quite peculiar. The liver of the pig that has recovered from a single large dose or from repeated smaller doses of this substance is a hob-nailed liver. This hob-nailed appearance seems to result from some degree of connective-tissue increase about the central and sublobular vessels with resulting contraction in these territories. It is, however, helped out by the fact that the liver cells are extremely large and hydropic, producing the effect of a swelling in the liver parenchyma. These changes are also associated with peculiar vacuolations that are particularly numerous about the central and sublobular vessels but are also present in other portions of the lobule. These spaces are filled, for the most part, with albuminous material, though they occasionally contain cellular detritus or a few red cells. Ascites is usually present.

In contrast to this group of central lesions, there are numerous substances that affect, by preference, the structures of the portal space and the periphery of the lobule. Most of these show a common type of action. In large doses, they produce complete necrosis of all structures in the portal space with a surrounding zone of liver cells. If the dose be reduced, however, the structures which manifest the greatest degree of injury are the bile-ducts. With even a small dose, a high degree of necrosis of bile-duct epithelium results while there is only a slight degree of fatty degeneration of the peripheral liver cells. Repair of lesions of this type takes place rapidly and is manifested by numerous mitoses in the bile-duct epithelium with an outgrowth of this epithelium toward the liver tissue and by marked proliferation of the connective tissue of the portal space. From this type of injury there results, therefore, a perilobular fibrosis which apparently interferes in some measure with the normal liver functions, as these animals always manifest a high degree of jaundice and frequently a pronounced ascites. In animals that recover from the early effects, some degree of absorption of connective tissue undoubtedly occurs, but the bile-ducts in the residue of this connective tissue are usually profuse, tortuous, and markedly dilated, indicating the persistence of some degree of bile-duct obstruction.

It is interesting to note in connection with lesions of this type that the most pronounced effect of the drug is produced by the first injection and that subsequently the dosage may be increased, even above the usual lethal limits, without materially altering the effects of the initial injection. Apparently, the tissue of this injured territory, once regenerated from previously injured cells, acquires a distinct degree of tolerance, or tissue fastness, and is not easily injured by further use of the drug. It is possible, however, to increase the dose until necroses again result. When such necroses are produced, however, they no longer involve the portal tissues or peripheral zone of the lobule but are localized beyond this territory, in the mid-zone of the lobule, and we are inclined to interpret this shifting of the point of injury as further suggesting a fastness of portal and peripheral tissues.

While speaking of the subject of fastness, it is perhaps well to call attention to the reverse of this phenomenon, namely, tissue sensitization. Many of the compounds that produce these peripheral lesions are compounds that also produce some degree of focal necrosis, and we have observed with some of them that, whereas a fastness of peripheral tissues may be produced by repeated injections, after a lapse of two or three weeks, the injection of a dose that previously produced scanty, if any, focal necrosis, will result in the production of innumerable such necroses. We know of no explanation that can be offered for this enormous increase in the focal effects of such compounds except to suggest a "sensitization" to this particular phase of the drug action.

Turning now to the kidney, this is the organ about which the greatest interest in the action of arsenic has centered, and one of the recognized types of experimental nephritis is that produced by the administration of arsenic. We have, however, not a single type of the arsenic kidney, but certainly two very sharply differentiated types with innumerable variations or gradations. The classical arsenic kidney, as is well known, is one that grossly may be described as a red kidney. On section, it exudes blood and shows a diffuse reddening from the outermost edge of the cortex to the pelvis, with little, if any, preferential action manifested in any of the zones of the kidney. There are numerous compounds of arsenic, the lesions of which conform more or less to this general picture. Some of these compounds, however, produce a greater degree of necrosis of tubular epithelium, while others exhibit a preferential action as regards the vascular changes, some producing the most marked alterations in the cortex, others in the medulla and still others showing hemorrhage and congestion confined almost entirely to the boundary zone. In some of the latter group, increase in the dose of the drug causes hemorrhage and congestion to spread through the cortex, while with others the extension is in the opposite direction.

A sharp contrast to the red arsenic kidneys is shown in a group of typically and extremely pale kidneys. With this group, there may be no evidence in the gross appearance of the organ of either hemorrhage or congestion, but on the contrary the tubular epithelium is involved to a very high degree. Connecting this group of pale kidneys with the typical red kidneys, however, comes a group of pale kidneys in which hemorrhage to a greater or less degree appears in the boundary zone. For example, arsacetin produces typically pale kidneys when administered intravenously in an amount sufficient to kill a dog in 24 hours. Atoxyl, when given in as small a dose as 20 mg. per kilo of body weight, produces a distinct and narrow

line of hemorrhage in the boundary zone of an organ that is otherwise quite pale. As this dose is increased up to the lethal limits, this line of hemorrhage spreads until it involves the entire medulla, converting it into what is essentially a blood clot. The hemorrhage also shows a tendency to spread outward, but to a far less degree, and usually the outer surface with some depth of subjacent cortex is distinctly pale, while the tubular epithelium shows marked necrosis.

Before leaving this subject, it is interesting to note also that the chronic lesions produced by these compounds of arsenic are localized and characterized according to the nature and seat of the lesions of acute poisoning. For example, compounds that produce acute lesions of the boundary zone are usually characterized in chronic stages by marked proliferation of connective tissue of this zone which, of course, may lead to secondary changes in the structures, both above and below. In all these types of renal injury, a remarkable degree of uniformity in the nature and seat of the lesion produced by a particular compound has been observed. These lesions, however, are susceptible to a certain degree of modification depending upon the size of the dose, the rapidity of action of the compounds and the length of life of the animal subsequent to the administration of the drug.

Another group to which we are inclined to attribute a great deal of importance is that of the lesions of the adrenals. The actual importance to be attributed to lesions of these organs is, of course, intimately related to their functional integrity. In the second place, no notice seems to have been taken of injury to the adrenal as a result of arsenical intoxication. We have found, however, that some degree and some type of adrenal injury are among the most constant changes produced by all classes of arsenicals. We may consider the evidences of injury from the standpoint of alterations in the lipoid content, structural changes in the cortex, structural changes in the medulla, and variations in the chromaffine content. All arsenicals that we have tested cause alterations in the physical character of the lipoids in the cortex of the guinea-pig. The fine droplets in which this lipoid usually exists, give place to larger droplets, especially at the outer and inner edges of the waxy cortex. The lipoid which is usually abundant in this zone then begins to decrease in the middle of the zone, but increases in both the zona glomerulosa and the pigmented zone of the cortex. With some arsenicals, this decrease and shifting continues until the waxy cortex may be practically free of all lipoids except at its extreme outer and inner edges; and finally, there may be no lipoid in the cortex except at the outer edge of the zona fasciculata. Corresponding to these changes in the nature and distribution of the lipoid we find a greater or less degree of degeneration, necrosis and disintegration of the cells of the adrenal cortex, and with some compounds hemorrhage is a prominent feature of the structural change. Regeneration of cortical cells after injury with most compounds is quite rapid, however, and numerous cells undergoing mitosis may be observed, especially in the outer half of the zona fasciculata.

In the medulla of the adrenal, the changes are equally striking; the most striking are perhaps those involving the chromaffine substance. While with some compounds of arsenic we have noted but little, if any, alteration in the chromaffine content, other compounds produce a very marked decrease in this substance. With some, the disappearance of chromaffine takes place early and quickly with rapid regeneration, while with others the early changes are but slight and it is only after some days that a distinct reduction in the chromaffine can be demonstrated. Another change observed in the medulla is of the nature of a round-celled or polyblastic infiltration, usually associated with some degree of endothelial and connective-tissue hyperplasia. The significance of this last group of changes is still uncertain, as we have observed similar changes, but of a less degree, in the medulla of animals after acute poisoning or even in controls. As I have said, injury to the adrenals seems to be common to all arsenicals, but here again it must be emphasized that the type and degree of injury vary very decidedly with different compounds and different animal species; and it has appeared to us that the measure of injury inflicted upon the adrenal by a particular arsenical was parallel with the susceptibility of a given animal species for a given compound.

The lesions described in these several organs can serve to give only a general conception of the diversity of lesions produced by different compounds of arsenic. The changes in other organs are equally varied and of just as great importance in their practical bearing, especially those of the nervous system and of the blood and blood-forming organs, the details of which cannot now be presented. One group of changes in connection with the pancreas may be cited, however, to emphasize the question of animal specificity. We have in our list of compounds a number of substances that produce widespread fat necrosis as a part of their characteristic action in mice and rats. With none of these substances, however, have we been successful in producing fat necrosis in guinea-pigs, only once in a rabbit and a few times in the dog, but in no instance was fat necrosis a constant manifestation of the drug action in any animal species except mice and rats.

So much for the lesions themselves which, undoubtedly, are of great importance in their bearing on pathological problems, but this is not the point from which we wish to consider them.

As I have previously indicated, injury is one of the standards by which we must gauge the value of our products and it is easily seen that upon this basis many compounds can be eliminated, at once, from the list of therapeutic agents, either on account of the seriousness of the injury produced by any or all doses of therapeutic quality, or because of irregularities in their action in different animal species, or of the frequency of irregularities or accidents that may follow their use in any species.

Fortunately, there are other compounds of a more hopeful character, and these require close inspection. In determining the therapeutic value of such compounds the attempt has been made to reduce this entire relationship to a numerical basis and to express the therapeutic value as the relation of the

dosis curativa to the *dosis tolerata* or $\frac{C}{T}$. In actual practice, such expressions are of but little value and are quite misleading, as neither of these values represents constants nor anything approaching a constant in most cases. Strictly, the *dosis tolerata* has been defined as the dose that evokes neither lesions nor symptoms, but in practice this standard has not been rigidly adhered to and the values usually given are hardly more than survival doses. In truth, it is doubtful if there is, as yet, a single compound of arsenic, possessing a *dosis curativa* against experimental trypanosermosis that produces neither symptoms nor lesions.

Further, such a basis of valuation implies a limitation of therapeutic standards to the efficacy of single dosage, or the method of *therapeia magna sterilisans*, and we are by no means prepared to concede that this is the only system of therapy or even the method of choice in all cases. The point of vital importance in determining the therapeutic value of arsenicals is the degree of injury that may follow curative applications of a given compound by whatever system it may be necessary to employ such a compound.

In weighing the pathological data, therefore, it is necessary to grasp clearly the relation between the method of employing the drug and the resultant injury, the difference between the characteristic lesions and the accidental lesions and the limitations fixed by these to the manner in which a given drug may be used. For example, there are compounds of arsenic which may be used in the theoretically curative dose with but slight recognizable injury. The usefulness of some of these compounds, however, is decidedly limited by the fact that repetition of even smaller doses may be attended by a pronounced accentuation of the injury, and in some instances an apparent sensitization occurs, giving rise to an increase in the frequency of accidental lesions produced by such compounds. On the other hand, some arsenicals permit of frequent repetition and even an eventful increase in the dose above the usual lethal limits with little, if any, increase in the injury produced by a single large dose. Instead of a dominant sensitization, we have here a rapidly developing tolerance or tissue fastness which tends to broaden the scope of usefulness of such compounds. Judged by the criterion of injury, therefore, the compounds of choice are those that manifest the most constant toxic action in all species of animals and permit of the greatest latitude of usage with a minimum of injury.

Since, from a constructive standpoint, the elimination of injury to the host is of prime importance, it follows, from what has gone before, that we must distinguish between toxicity and tissue injury, because it now appears that one may be diminished without necessarily reducing the other. It seems, indeed, that each compound of arsenic is capable of setting up a lesion-complex which is definite, although more than one compound may produce nearly identical lesion-complexes; in the complexes, moreover, the lesions of one or possibly two organs are dominant. This being true, it follows that the lesion-complex is measurably related to the chemical constitution of the compound, from which fact it follows further that the determination and study of the lesion-complexes must inevitably influence the construction of therapeutically active drugs. But our present knowledge of how to remove the defects of chemical compounds is limited in the extreme. The outlook is hopeful, however, that as clinical and experimental experiences increase in number and precision, a rational basis of procedure may emerge.

In conclusion, in presenting this seemingly unpopular phase of specific arsenic therapy, the subject has been considered entirely from the view-point of the experimental worker. The achievements in this field of work have been truly marvelous and we must emphasize the fact that we do not wish to detract, in any way, from the value of these achievements to clinical medicine nor to create any unfavorable impression against arsenic therapy. On the contrary, we wish merely to emphasize the importance of a thorough knowledge of the lesions produced by compounds of arsenic in all their bearings as a means to an end, namely—the successful prosecution of the problem of specific arsenic therapy.

DISCUSSION.

DR. WELCH: I have been extremely interested in Dr. Brown's studies. They illustrate the opening up of a very broad and new field for exploration by studies in chemotherapy. He has given us a sketch of the history and I do think that Ehrlich is the one who grasped the full, broad significance of this line of investigation, partly by his insistence on the conception of the specific action of these chemical compounds upon definite tissues. One could not have foreseen, any more than he could from his early studies in immunity, where it was all going to lead us. No one could have predicted from the early studies in immunity what a vast territory was being opened up, a territory of the broadest interest, some practical and some of wide biological significance—a fascinating field of study, with its own literature and special workers who have made it their life work. Now, here in chemotherapy we have opened up another great territory with interests far beyond anything that could have been conceived.

Dr. Brown has told us about only one side of the very interesting and elaborate studies going on in the Rockefeller Institute in this direction. The ultimate aim of course is to see if improvement cannot be made in the chemical remedies. Dr. Brown has pointed out the most extraordinary lesions, some of which have perhaps no analogy at all in human pathology. It has really been demonstrated that some of these new synthetic chemical substances place in our hands the means of studying certain problems in general pathology in the most fascinating way. Some time ago Ehrlich handed me a drug, without telling me of what it was composed, which injected in small quantities into the tail vein of a mouse (an operation requiring a little skill) produces the most amazing anasarca. Just think of having a substance which injected into the circulation will produce this anasarca. I gave the drug to Dr. Evans, who repeated and confirmed Ehrlich's results.

I think Dr. Brown has gotten some organic substance, which so far as I can judge from the pictures, produces quite interesting lesions—lesions with which we are unfamiliar in human pathology. It also seems to be something which produces genuine cirrhosis, a condition which more closely resembles human cirrhosis than anything I have seen.

The whole field of experimental nephritis is one that has been most actively studied of late years. Dr. Pearce and his colleagues, Dr. Opie and others, all started with the idea that you could produce by certain drugs and poisons lesions of the kidney, which

in one instance were exclusively tubular, in another exclusively vascular or exclusively interstitial. In human beings it never seems to be safe to infer that you have exclusive tubular or other lesions. Arsenic is ranked among the poisons that belong to the vascular group, whereas uranium, the chromates, and others, produce necrosis of the cells. Dr. Brown has evidently gotten some arsenical compounds which produce mainly the predominance of tubular lesions, quite unlike the nephritis which has hitherto been attributed to arsenic.

In this field of chemotherapy, the study cannot be made quite so simple as the distinction between *dosis curativa* and *dosis tolerata*. Although Dr. Brown did not elaborate the fact, it must be patent to everyone that very severe toxic lesions are produced by certain doses, for it is a familiar fact that one and the same substance given in minute or small quantities may be an admirable stimulant or curative, and at the same time act as a very severe poison in other doses. I do not think this necessitates very depressing views as to the possibilities of arsenic therapy. It is very interesting to know of these lesions.

I wonder if Dr. Janeway may not be able to give us, from the human side, his experience as to the toxic effect of some of these arsenical compounds.

Dr. Janeway: It has been a very great pleasure to me to see the demonstrations of Dr. Brown's specimens. I had known of the work but had not had an opportunity to see the actual lesions. These things have a very important bearing which is being borne in on us more and more every day as we meet with unexpected toxic effects of salvarsan. We have this winter seen quite enough to convince us of the desirability of knowing the types of lesion which salvarsan may produce. In particular, many of you who have been present at the Saturday clinics may remember the Hindu, who as the result of an apparently safe dose of salvarsan, developed the most intense renal lesion, with blood in the urine, marked oliguria, œdema and in addition jaundice with a swollen liver, which still persisted when he left the hospital in fair convalescence at the end of nearly two months. At one time I feared he was going to have acute yellow atrophy of the liver. He evidently had extensive necrosis within the liver, possibly the type of lesion which Dr. Brown has shown in the portal spaces. That seems quite a possibility. Our renal lesions have been more frequent than hepatic lesions. Renal lesions plus general reactions have been our greatest bug-bear in the use of salvarsan therapy.

I have wondered to what extent the hemorrhages Dr. Brown obtained were really a specific manifestation of the drug. I once saw a case which made me feel that possibly it was not only the nature of the irritant which determined renal hemorrhage. We had a young woman in the City Hospital, who had a subacute nephritis, whose only discoverable cause was the existence of an active syphilis. At autopsy, she had on one side a perfect example of the large white kidney, with extensive degenerative tubular lesions; on the other side a perfect example of the hemorrhagic type of nephritis. The kidney actually dripped blood and was a mass of hemorrhages. The different lesions in the two kidneys in this patient were apparently due to the same circulating poison.

Dr. Rowntree: Having at one time worked in the fields of chemotherapy, Dr. Brown's work has been peculiarly interesting to me. It pleased me a great deal to hear him give Thomas so much credit for outlining the fundamental principles of chemotherapy.

The introduction of salvarsan, Ehrlich's greatest achievement in this field, is usually accredited to the fact that he forsook the pentevalent and worked with the trivalent form of arsenic. In view of the almost infinitely greater trypanicidal value of the latter, it is peculiar to find that there is no corresponding striking difference in the pathological lesions produced by the two forms.

Dr. Brown demonstrates a tissue specificity in response to drugs. Other forms of specificity impress the worker in these lines. Trypanosomes of various strains will all be killed by certain antimonials; whereas spirochetes, which are biologically closely allied, under the same conditions will not be affected at all. Several points come under consideration; specificity of the infecting organism, specificity of tissues and specificity of species. The marked variation in the pathological picture in different species may in part explain the variation of tolerance in different species and the variation in the lethal dose of a drug.

Some years ago Dr. Abel and I studied the effect of some antimony preparations on trypanomiasis in various laboratory animals. We found it was possible to get an active trypanocidal agent which could be given repeatedly in large doses without any apparent injury to the host. It was easier, however, to obtain results in small animals, such as rats and mice.

Dr. Wade H. Brown: In reply to Dr. Rowntree, these lesions were all from pure toxicity experiments—no infection existed. Mention was made of differences in toxicity in different animal species. In some instances these differences were very striking and they are important in connection with the great differences that prevail in the system of testing the trypanocidal action of drugs in different laboratories. For example, the Germans rely mainly on mice, the English lay stress on the use of rats, while the French have used a greater variety of animals, mice, rats and guinea-pigs. Thus, many difficulties arise in the interpretation of results. Some think that the results with mice mean very little and that those from rats are much more important, while still others lay greater stress on the results obtained in guinea-pigs. I think, as a matter of fact, that none of these views are wholly correct. I do not believe there is any one species which tells the story. I think the only rational procedure is to use several species and large series of animals. As it happens, we have had our best curative results with the guinea-pig—an animal with which others have not been able to obtain their best results. Our results may be referable to the better tolerance of guinea-pigs for the arsenicals we have used.

As to the question Dr. Welch asked in regard to the specificity of any of these compounds for the vascular system or the tubular epithelium of the kidney, I do not believe we have as yet any arsenical that we can say is specific for one tissue or the other. As a matter of fact, there is always a combined action, but vascular injury of some description is far more common than epithelial injury.

I tried at the conclusion of my paper to emphasize the fact that this presentation was from the standpoint of some of the difficulties that the experimental worker has to contend with. I think there is nothing anywhere that should be interpreted as disadvantageous to the practice of specific arsenic therapy. There are some facts, however, we should know as clinicians as well as experimental workers. The effects described are the exaggerated effects brought out in the host by toxic doses. In many instances the therapeutic dose is far below these doses and produces very little injury, as far as we can determine.

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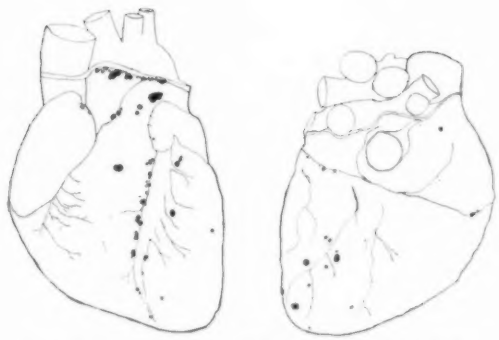
FIG. 1.—Large lymph-glands: (*a*) About the base of the heart and great vessels from which retrograde infection of the epicardial lymph-channels took place. (*b*) Minute blastomycotic nodules along the perivascular lymph-channels.



FIGS. 2 and 3.—Illustrating the distribution and relative size of the minute focal lesions along the course of the lymph-channels. Fig. 2, the front; Fig. 3, the back of the heart.

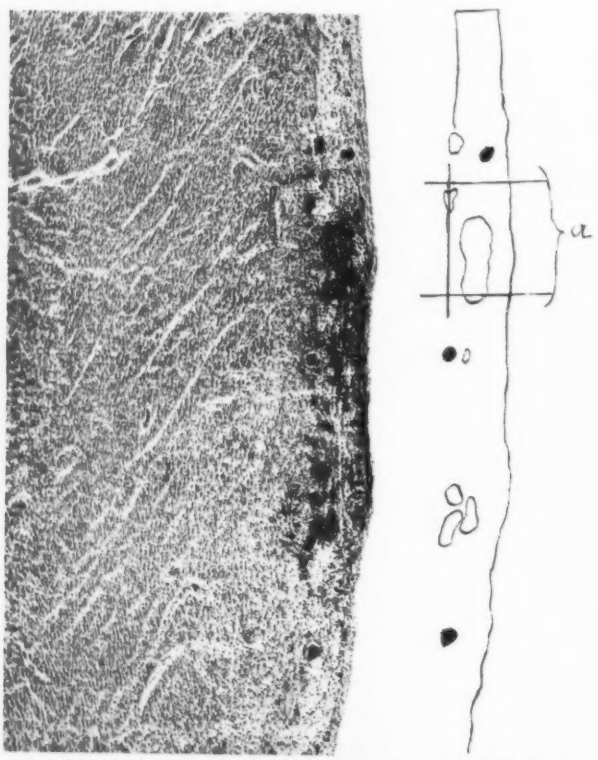


FIG. 4.—Miliary subepicardial blastomycosis. Photomicrograph, 35 diameters. In the chart to the right, the region *a* is that shown in Fig. 5. The lymph-channels crowded with blastomycetes are outlined empty; the blood-vessels are shaded solidly black. In the photomicrograph they look alike.

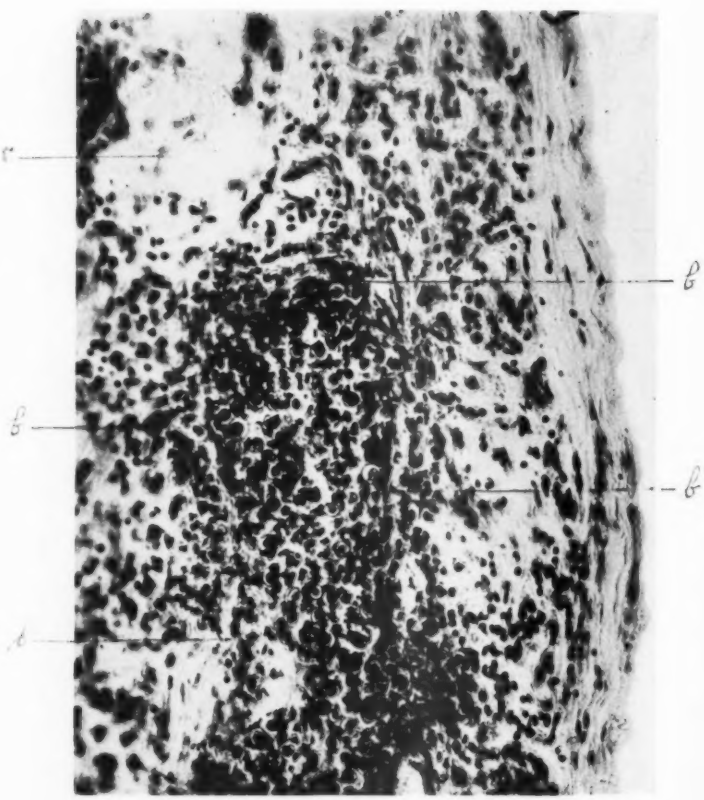


FIG. 5.—The large lymph channels containing many blastomycetes shown in the area (a) of chart to Fig. 3. In this Fig. 5, the lines (b) are drawn to the edges of this lymph channel. (c) Subepicardial adipose tissue. (× 275.)

MILIARY BLASTOMYCOTIC RETROGRESSIVE LYMPHANGITIS OF THE EPICARDIUM.[1]

By E. R. LECOUNT.

(From the Pathological Laboratory of Rush Medical College.)

In most of the summaries in medical literature of the various contributions to our knowledge of systemic or generalized blastomycosis, comparisons have been made between this disease and coccidioidal granuloma, which it greatly resembles, and attention has been especially directed to the greater frequency with which the lymphatics, both glands and channels, are involved in the latter disease.[2] With greater opportunity to examine conditions in systemic blastomycosis, it has been learned that infection of the lymph-glands is by no means rare, although the disease is disseminated throughout the body by the blood; also that the changes in the lymph-glands are definite, grossly evident and closely resemble those caused by tuberculosis.[3] Stober and the writer have repeatedly found the lymph-glands involved in regions adjacent to extensive blastomycosis. Stober says: "A general enlargement of the lymph-glands was found at necropsy in about one-third of the cases (29), and blastomycotic lesions, in addition to having been found in the peribronchial lymph-nodes a number of times, were on two occasions in this series also found in the submaxillary, axillary and inguinal glands."[4]

Bassoe[5] found changes in the mesenteric and retroperitoneal lymph-glands characteristic of blastomycosis, associated with extensive amyloid degeneration, but without fungi.

That the similarity to tuberculosis extends even to the occurrence of retrograde dissemination along lymph-channels is illustrated by the following observation:

In 1911 a Bulgarian laborer, age 25, entered the Cook County Hospital to the service of Dr. Amerson with a cellulitis of the left arm which yielded to boric acid fomentations and to external applications of iodin and ichthyol. The cellulitis was of two months' standing; there was a sharply localized swelling just below the cubital fossa on the front of the arm and on the wrist a healing abrasion; there was no lymphangitis demonstrable connecting these two lesions. The man remained in the hospital eight days and was discharged much improved and at his own request.

A year later, a Bulgarian laborer, 26 years old, with the same name, entered the same institution to the service of Dr. Ormsby. He had been sick for three months with a cough, fever and multiple abscesses and ulcers on the body, which were quite promptly recognized as blastomycotic; and in the pus of one of them the organisms were found. He walked or was helped by a friend into the hospital, but died two hours after entrance.

Both of these Bulgarians talked very brokenly and accounts of their illness were obtained with difficulty. Up to the present time attempts to learn more regarding them have been fruitless, notwithstanding the kind help of Dr. Dosu Doseff, one of the Chicago Bulgarian physicians. From the correspondence in name and age, however, it is to be assumed that the two persons were in reality the same individual. From the post-mortem examination made 16 hours after death, the following data were obtained.

Anatomic Diagnosis.—Miliary, submiliary and nodular blastomycosis of the lungs; miliary and nodular blastomycosis of the tracheo-bronchial and mediastinal lymph-glands with abscess formation; multiple blastomycotic ulcers of the skin; healing and unruptured subcutaneous abscesses; nodular blastomycosis of the spleen and kidneys; miliary blastomycosis of the pericardium and peritoneum; blastomycotic abscess of the pancreas; marked emaciation and anæmia; small decubital necrosis over the sacrum; fibrous (left) pleuritis; hyperplasia of the axillary retroperitoneal and mesenteric lymph-glands; fibrous adhesions between the colon and under surface of the liver, between the transverse colon and the posterior surface of the stomach; stellate white scar in the meso-sigmoid; ossified costal cartilages.

Some idea of the extent of the disease may be obtained from the following account of the external appearances:

There are on the body (1) numerous regions in which there are unbroken abscess cavities, soft and fluctuating; (2) other regions where the skin over these has necrosed regions, round, elevated and containing soft necrotic material, and (3) regions which are similar to the last mentioned, but which are healing, covered with thick dark reddish-brown crusts.

These various lesions vary in size from a millet-seed to 4 or 5 cm. in diameter and are found as follows: on the forehead, about the external occipital protuberance in the scalp tissues, in the skin of the neck; about 12 on the face; a large lesion about the right nipple; many small ones over the front of the chest and over both arms; on the left hand at the base of the thumb and over the outside of the left wrist one each; numerous small ones on the back; one opposite Scarpa's triangle of the right thigh; small lesions on the front and back of each leg; large ones in the skin of the front of the right thigh, the inner surface of the left foot, and behind the ankle.

The left hand and foot are encased in surgical dressings and under another dressing there is a region 6 cm. long and 2.5 cm.

[1] Reported at the 13th annual meeting of the American Association of Pathologists and Bacteriologists in Washington, May 6, 1913.

[2] See for example, S. Hektoen, "Systemic Blastomycosis and Coccidioidal Granuloma." Journ. Am. Med. Assn., 1907, XLIX, 1071-1077.

[3] See descriptions and illustrations in "Systemic Blastomycosis." E. R. LeCount and J. Myers: Journ. Infect. Dis., 1907, IV, 187-200.

[4] Systemic Blastomycosis. A report of its pathological, bacteriological and clinical features. Arch. of Int. Med., 1914, XIII, 545.

[5] P. Bassoe: Disseminated Blastomycosis. Report of a case involving the lungs, lumbar vertebræ and subcutaneous tissue, with multiple abscesses and fistulæ and extensive amyloid degeneration. Journ. Infect. Dis., 1906, III, 97.

wide, on the outside of the lower third of the left leg, where the skin is absent, exposing gray necrotic subcutaneous tissues. The border of this place is rough and irregular, soft, easily torn and bluish-red. Fourteen lesions are more than 1 cm. across; altogether they number 110.

When a careful examination was made of the heart, conditions of unusual interest were found, reminding us again that any post-mortem examination of the body of a person dying from systemic blastomycosis may reveal changes new to pathological anatomy.

The heart has about 100 lesions easily seen by gross examination of its external surface.[6] Their distribution along the course of the blood vessels, especially the anterior coronary vessels, is shown in Figs. 1 and 3. They vary from 0.5 to 6.5 mm. About half of them are from 2 to 6.5 mm. in diameter, the largest 4 by 6.5 mm. They are firm, pinkish-brown, generally paler than the adjacent muscle, and round, oval or irregular from coalescence. Most of the lesions are elevated 1 mm. or less; about a dozen and including some of all sizes are slightly, if at all, elevated.

The involvement of the lymph-glands about the bifurcation of the trachea and root of the aorta (Fig. 1) is marked, even greater than I have described in another place with Myers.[7]

[6] I am pleased to acknowledge my indebtedness to the great care taken by Dr. Mary Mitchell in charting the lesions for Figs. 2 and 3.

[7] *L. c.*

The changes in them are similar with a striking resemblance to tuberculosis in both the gross and microscopic alterations.

The blastomycetes were recovered in pure culture without any trouble from the pus in an unbroken subcutaneous abscess removed at the post-mortem examination.

Microscopic Examination.—In a number of the epicardial lesions the conditions are quite similar. They stretch along the outside of the heart in the deeper parts of the epicardium in their beginnings and have their origin in an extension of the disease along the lymph-channels.

Only the very superficial parts of the myocardium are involved. The nodule illustrated in Fig. 4 is a little over 2 mm. long in the section photographed for this illustration and 0.2 to 0.5 mm. wide in the various sections examined of the series through it. As the peripheries of the lesions are approached in studying them, the blastomycetes, which are very abundant, become limited to small lymph-channels; when traced back again into sections where the most marked changes are present, these lymph-channels become increasingly difficult to follow (Fig. 5). In such sections the lymph-channels usually occupy the centers of the lesions. These lymph-channels contain no red blood corpuscles in any of the sections. The necrosis in these minute blastomycotic abscesses is slight, the cellular exudate being largely formed by mononuclear cells.

AN OCCASIONAL FEATURE IN THE PATHOLOGY OF SPLENOMEGALY.

By Thomas P. Sprunt, M. D.

The lesion which forms the basis of this note has been described in the spleens from cases of Banti's disease or similar conditions by Marini[1] (1902), Stengel[2] (1904), Simonds[3] (1908), and by myself[4] (1911). Somewhat similar appearances are only very briefly mentioned by Hamill[5] (1902), and by Borissowa[6] (1903). Kockel[7] and Bittrolff[8] have described analogous processes in the lungs in chronic passive congestion and in pernicious anæmia.

Microchemical studies[4] have shown that we have to do with a selective impregnation of elastic tissue with the phosphates of calcium and iron, giving rise to ochre-colored patches about as large as grains of wheat and easily visible to the naked eye on incising the spleen. They have a characteristic microscopic appearance with moderate magnification, best indicated by the accompanying illustrations (Figs. 1 and 2).

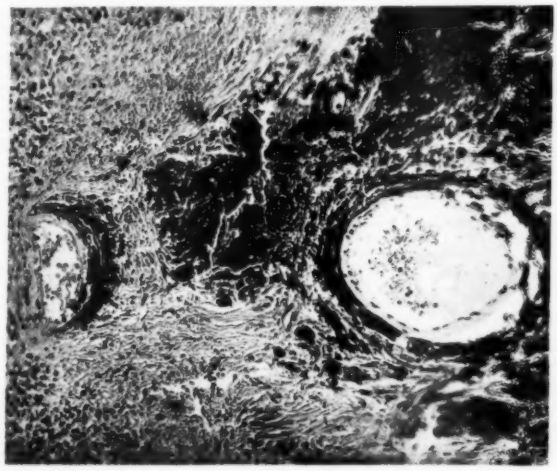
My interest was again aroused in this connection by the occurrence of another case which showed this peculiar feature, and by the report of Gibson[9] who describes in several spleens from different diseased conditions what is evidently the same lesion, and attributes to it etiological importance, considering these areas agglutinated masses of organisms of the nature of a streptothrix. His description and particularly the illustrations which accompany his paper leave no doubt that we are dealing with the same pathological process. His opinion was based solely upon morphological evidence and strengthened by certain staining reactions; but in spite of this insufficient evidence, it has excited a considerable degree of interest in a few workers in this clinic, has been mentioned editorially by journals[10] in this country, and is quoted in a recent article by Bunting and Yates[11] as evidence in favor of the infectious nature of splenic anæmia.

Several forms of splenomegaly are undoubtedly of infectious origin, notably the tuberculous, the syphilitic, and those occurring in chronic streptococcus infections. Recent work[12] indicates that the leukæmias are probably of an infectious nature. Perhaps in the future it may be demonstrated that the more obscure forms of splenic enlargement, such as the group comprising the splenic anæmias and Banti's disease, belong in the category of infectious processes. Such a demonstration, however, must rest upon more convincing evidence than suggestive morphological appearances, which admit of more than a single interpretation. Because of the probable misinterpretation which Gibson has placed upon the lesions studied by him, it has seemed desirable to call attention again to the exact nature, morphological and chemical, of such lesions in the spleen.

The ochre-colored patches are found microscopically to consist of narrow golden or hematoxylin-staining bands arranged concentrically in the walls of small vessels having a diameter of from one-tenth to one-sixth of a millimeter and, in addition,

of broader similar bands less regularly arranged in the nearby trabeculæ. Between these coarse strands, fine yellow or dark staining filaments form a delicate network which is naturally emphasized by Gibson, who was impressed by its resemblance to a fungus. The club-shaped extremities of some of these filaments, which he describes, are easily made out and such appearances may be found unassociated with the more striking coarser lesions.

All this material stains readily in the tests for iron; it is easily dissolved and disappears from the sections when treated with dilute mineral acids or stronger oxalic acid, leaving a hyaline area which stains very poorly, gives the so-called "elacin" reaction of Unna [1] but does not take the usual elastin stains. The most instructive preparations are made by first treating sections with potassium ferrocyanide and hydrochloric acid and then staining with orcein. By this method the iron-containing tissues are colored blue and the elastic tissue a silky brown, and such preparations show very well



Journ. of Exper. Medicine.

FIG. 1.—Heavy accumulation of the incrusting salts. (Hæmatoxylin and eosin.)

the apparently normal brown fibers running over into the wavy blue fibers, which still retain some of the characteristic morphology, but are continuous with the dark blue, straight, broken bands in the center of the lesions. The transition is especially well shown in the fine filamentous network, where the two stains can be seen coloring the same fiber in different parts of its course.

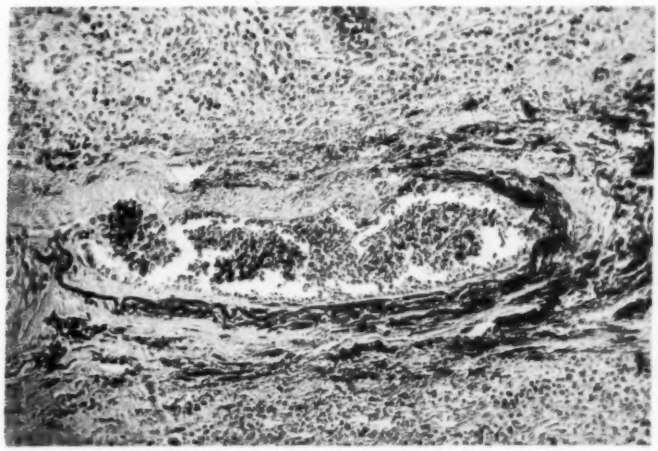
As already remarked, all this material is quickly removed from sections by dilute mineral acids, even by the small amount in the ordinary elastic stains (less than 1 per cent), unless the iron has first been converted into Prussian blue.

On the other hand, the several strains of streptothrix organisms which I have tested may be exposed to 10 per cent mineral acids for over an hour with little or no change in their staining reactions.

Further microchemical details may be obtained by reference to the articles already mentioned, and a comparison of the illustrations accompanying the several papers will convince the reader of the unity of the lesions described. There is no local inflammatory reaction whatever about these structures in the spleen, although in the analogous condition in the lung, found in rare cases of chronic passive congestion, Bittrolff reports a very definite foreign-body reaction with numerous giant cells which contain fragments of the incrusted fibers.

The recent case showing this peculiarity is here briefly reported through the kindness of Prof. Finney:

The patient, a white man, from Georgia, aged 30 years, was admitted to the hospital on June 18, 1913, complaining of "splenic anæmia." He gave a fairly definite alcoholic history, and had had what may have been a chancre in 1903 without any subsequent development of secondary lesions. He suffered from a left hemiplegia for nine weeks in 1904. He dated the present illness from July, 1911, when, after an attack of "malaria" of three weeks' duration, his spleen remained large. In September, 1912, there occurred a convulsion, after which he was unconscious for thirty minutes. In November, 1912, January, 1913, and May,



Journ. of Exper. Medicine.

FIG. 2.—Lesion less marked. Note different stages of process in internal elastic lamella. (Hæmatoxylin and eosin.)

1913, similar attacks were experienced. In May there was also a severe attack of pain over the liver continuing four hours; and again in June one still more severe. He had taken thorough courses of quinine with no effect on the symptoms or spleen; similarly, large doses of mercury, iodides and sodium cacodylate had been without apparent effect on the size of the spleen.

Examination revealed a moderate pigmentation of the exposed parts, pyorrhœa alveolaris, a scar on the penis, a very large spleen, and an apparently small liver, flatness stopping 5 cm. above the costal margin in the mammillary line. There was no general lymphnodular enlargement and nothing to indicate a lesion of the central nervous system.

The urine was normal; the blood pressure 115 mm. Hg.: the temperature varied from 98 to 100° F., reaching the latter point twice in 12 days; the pulse rate was about normal. The Wassermann test was negative. The blood examination showed no anisocytosis nor poikilocytosis; red cells, 2,500,000; leucocytes, 1,160; hæmoglobin, 40 per cent. Differential count of leucocytes; polymorphonuclear neutrophiles, 73.6 per cent; eosinophiles, 2.4 per cent; basophiles, 0.8 per cent; small mononuclears, 15.2 per cent; large mononuclears, 6.4 per cent; transitionals, 1.6 per cent.

Of tuberculin tests, the Calmette 1 per cent and 5 per cent were negative; the von Pirquet test was positive.

On June 30 splenectomy was performed by Dr. Finney. After the operation the temperature remained about 102° F., occasionally rising to 103°. A small stitch abscess developed in the wound, and there were signs of a pleural effusion on the left side with a moderate leucocytosis. After a thoracentesis (400 cc. of clear fluid) his condition gradually improved, but the patient left the hospital against advice before his temperature had become normal.

The spleen was adherent only to the tail of the pancreas. It was quite large, measuring 22 x 9 x 13 cm. The consistence was somewhat firmer than usual; on section the cut surface was dark greyish-red, fairly smooth, with widely spaced Malpighian bodies and rather prominent trabeculæ, in which could be seen scattered here and there the small ochre-colored patches, 1 to 3 mm. in diameter, usually surrounded by a purplish zone. Microscopically, the spleen was the counterpart of the one already described.

The occurrence of these lesions in the spleen, removed at operation and examined immediately in the operating room, disposes effectually of Hueck's " criticism that such findings are due to the post-mortem absorption of iron.

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MICHAEL SERVETUS.

DISCOVERER OF THE PULMONARY CIRCULATION.—HIS LIFE AND WORK.

By John C. Hemmeter, M. D., Phil. D., Sc. D., LL. D.,

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Estimated from the standpoint of our prevailing conceptions of evolution and heredity, the human being is to be regarded as the product of his environment. In proportion to the physical perfection of the environment, the richer its elements of geographical charm, beauty and healthfulness of climate, the more varied its range of accessible food products, in the same degree its human inhabitants should develop into a nobler type. As the high priest in Mozart's " Zauberflöte " idealizes the thought in song:

" In diesen heiligen Hallen
Kennt man die Rache nicht
Und ist ein Mensch gefallen
Ruft Liebe Ihn zur Pflicht."

The human being may be assumed to develop a purer and more admirable form of physical and psychical excellence in accordance with the natural conditions that surround him. Yet the physical universe, even when revealed in its most lovely aspects, does not always tend to the ennobling and elevating of those who are constantly exposed to its power. Despite its grace of outline, the rapture that abides among its lonely hills, its misty mountain tops, the dawning sun that furrows all the orient into gold, "while every prospect pleases," man retains his original vileness:

" Die Welt ist zufrieden überall;
Wo der Mensch nicht hinkommt mit seiner Qual."

Among the master works of the Divine Artist, the Lake of Geneva assumes a foremost place. From every point of view, geographical, historical, literary, its shores are rich in complex memories and associations, tracing back for more than 20 centuries to the time described by Julius Caesar when he met the Helvetian host at the bridge over the Rhone, and broadening through the slowly forming ages until we reach the periods forever linked with the names of Calvin, Knox, Servetus, Voltaire, Rousseau, Gibbon, Madame de Stael, Byron, Ruskin. Mt. Blanc looks down from the region of Savoy and its evening glow lights up the lake with a brilliance that neither art nor language has been able to portray. Yet it was in Geneva that there was enacted one of the most deplorable tragedies that have darkened the annals of the modern world—the death of Michael Servetus at the stake on October 27, 1553.

Apart from the sphere of the scientist and the student of theological development, the name of Michael Servetus is almost unknown to our contemporary world, and when introduced, save in the esoteric circle of the medical investigator, it is suggestive only as an echo of a vanished age. Yet no name in the long record of scientific evolution is more worthy to be rescued from the oblivion which has enveloped it and to be brought into the clear light of our modern day. Servetus may be regarded as marking one of those distinctive processes or

advances by whose agency or activity science in all her phases "slowly broadens down from precedent to precedent." The range of his acquirements seems to have embraced every form of learning in his age, accessible or available. In a measure, at least, he had realized the ideal of Francis Bacon and taken all human knowledge as his province. In the field of medicine he revealed a creative power which heralded the coming of the modern era; his skill in polemic theology was unsurpassed—subtle, acute, penetrating; and with these rare qualities of intellect, was blended the charm of a noble and generous spirit. Yet, with all these graces of heart and intellect, he became the victim of the prevailing bigotry and intolerance which characterized every form of religious thought, Catholic or Protestant, and through the resistless power of Calvin, the political, as well as the theological, autocrat of Geneva, he suffered death at the stake.

Now that the Reformed Churches of France and Switzerland have erected at Champel, the scene of his martyrdom, an expiatory monument to the memory of Servetus and the people of Vienne[1] have perpetuated in marble or bronze their reverence for his genius and their commiseration for the tragedy of his death, the obligation becomes more imperative than ever to reveal the truth of his history; to dispel the errors and fabulous assertions with which passion and intolerance have obscured his fame, and to exhibit in abiding clearness the record of the scientific discoverer, the harbinger of the modern world in the field of medical exploration in relation to the circulation of the blood. To accomplish this purpose, we shall freely avail ourselves of the invaluable record of the Abbé d'Artigny, Canon of the Cathedral of St. Michael's at Vienne, who had also at his disposal, during the time that he was engaged in the preparation of his Memoirs, the archives of the archbishopric of Vienne, then preserved in complete condition. His statements, derived from so eminent a source, will hardly be called in question by the most sceptical inquirer, or the most hostile student of the life of Servetus.

The most authentic accounts represent Servetus as having been born at Tudelle in Navarre in 1511. The date is inferred from the reply which he made to his judges at Vienne in April, 1553, declaring himself at that time to be 42 years of age. The most accurate and trustworthy biographers represent him as having been born at Villanueva-on-Aragon, as at a later period he assumed, in accordance with the usage of former ages, the name of his birth-place, calling himself Michael de Villeneuve. When at a subsequent time he was reproached by Calvin for concealing his name, he justified himself upon the ground that he had assumed the name of his native city. Yet, when arraigned in Vienne, he declares to the judges that Tudelle is his native city. The discrepancy, however, is more in appearance than in reality and can be explained upon the natural supposition that the ancestors of Servetus came originally from Villanueva and afterwards acquired a residence in Tudelle. During the age of Servetus and for centuries preceding, patronymics and local designations were used without the definite and precise significance characteristic of a later time, being modified or varied as changes of place or condition might render desirable or expedient. As the surname did not affect the issue of the trial, some such cause as we have suggested will present a plausible reason for the change. His real name, Servetus, was one that he deemed it prudent to conceal from motives of a nature such as readers of "The Antiquary" will readily recall. During the entire judicial procedure he is addressed as Michael de Villeneuve, the title he had assumed in France. Even within a comparatively recent period Coleridge and Poe, upon entering the military service, disguised their identity by the assumption of pseudonyms.

From early childhood, Servetus displayed a rare intelligence and a marked fondness for the attainment of knowledge. So devoted was his application to study that at the age of 14 he had acquired the elements of Latin, Greek and Hebrew, also an accurate acquaintance with mathematics and the crude mechanical philosophy of the time, as well as the scholastic theology, then recognized in the universities of Europe as the embodiment and the vital essence of religious truth. The study of Holy Scripture and his mode of interpreting its teachings in reference to the Trinity was the specific cause that aroused the antagonism of Calvin and "marshalled him the way" to the stake at Champel. According to his biographers, the father of Servetus, who was by profession a notary, sent him to Toulouse in order to devote himself to the study of law. The reputation of the ancient city for sanctity had gone out into all the medieval world and the fame of its holiness was blazoned by the inscription placed over the vault which was reputed to contain the bones of seven of the twelve apostles, "Non est in toto sanctior orbe locus." More than two centuries later than the time of Servetus this hallowed center of apostolic tradition became the scene of the Calas tragedy (1762), more atrocious in spirit and more ghastly in detail, if such be conceivable, than that enacted at Geneva in October, 1553. If the testimony of Servetus himself is to be accepted as trustworthy, he did not imbibe his heretical opinions in regard to the doctrine of the Trinity during his student days at Toulouse. His inoculation with this fatal heresy may be assigned with probability to a later period and its origin traced to the influence of his sojourn in Italy, which brought him into contact with the prevailing theological tendencies of the country, notably at variance as they were with the orthodox or accepted interpretation of the mystery of the Trinity.

According to the declaration of Servetus, he entered the service of the Holy Roman Emperor, Charles V, of Germany (also King of Spain under the title of Charles I), at the age of 15 years, a circumstance which enables us to fix the year definitely as 1526, he having been born in 1511. He seems to have been associated in some capacity with the confessor of the Emperor, and was present when Charles was crowned at Bologna instead of Rome in 1530, assuming the title of King of Italy, as well as that of Emperor. That Servetus had been in Italy was known to his biographers, as he refers to it in the preface to the first edition of his "Ptolemy," but the contemporary political events with which he was associated by virtue of his relation to Charles V make it possible to fix the duration of

[1] Vienne in the Department Isère, France.

his residence with at least approximate accuracy. Trinitarian heresies, among the earliest to reveal themselves in the development of theological dogma, were at this time rife in the cultured circles of Italy, now prostrate under the power of Charles V. The intellectual vigor of Servetus, as well as his critical acquaintance with the scholastic philosophy and the method of disputation prevailing in the universities, assured him a conspicuous place in the polemic combats of the time, when the dawning reformation and its novel teachings were the absorbing and almost exclusive theme. Luther had confronted Charles V at Worms only a few years preceding the coming of Servetus into Italy, and the thought of the world was concentrated with eager and ever-broadening interest upon the attitude and the innovations of the Monk of Wittenberg. In accordance with the law of evolution in the sphere of theology, the accepted doctrine of the Trinity was selected as one of the vital points to be assailed and Servetus was chosen by general consent as the protagonist who was to deliver the first blow. Although a youth of 18, he had devoted himself to the preparation of his treatise, "De Trinitatis Erroribus," his relentless antagonist, Calvin, being at the time only 20. De Quintain or Quintana, the confessor of Charles V, being called to Germany, Servetus accompanied him, it being understood, however, that he was to maintain an intimate relation with his Italian associates through the medium of correspondence.

The following year (1531) De Quintain, the confessor, died, and Servetus found himself without guide or monitor in the perilous realm of theological controversy. His great native force and energy of will revealed themselves in his determination to establish himself as a reformer—another aspect, it may have been, of that same creative and originative spirit which assured him an abiding place among the harbingers and heralds of scientific discovery in the still broadening field of medical research. At Basle he held conference with Occolampadius, and at Strassburg he became involved in controversy with Capiton and Bucer, the latter one of the foremost lights of the expanding Protestant Reformation, the Trinity and the doctrine of consubstantiation being the special themes involved in the discussion. These two doctrines Servetus combated with the utmost tenacity, as well as acrimony, his violence so offending his adversaries that Bucer, though inclined to moderation and self-restraint, assailed him with the greatest vehemence, even going to such an extreme as to declare that he "deserved to be cut into pieces and to have his entrails torn out" (Lib. II, pp. 56-60).

The first work of Servetus, entitled "De Trinitatis Erroribus Libri Septem per Michaelum Servetum," was published in 1531. He was at that time only 20 years of age. Newton was three years older when he first promulgated his theory of gravitation. Bryant, Keats, Rossetti, Tennyson produced the early poems upon which their fame in a measure still abides between 18 and 20. In his first work Servetus assails the doctrine of the Trinity, characterizing the union of the three divine persons as a mere fantasy, a chimera, gods devised by the metaphysicians. The orthodox teaching was cast aside as irrational and impossible, having no foundation save in the ignorance of theologians. During the succeeding year (1532) he issued at Hagenau a second treatise relating to this subject, entitled "De Alegoramunde Trinitate Libri Duo," but being devoid of financial resources and having been expelled from the communion of the foremost reformed churches in Germany, he established himself in France. One of his special aims was to pursue the study of mathematics, but above all to devote himself to the science of medicine. With this end in view, he placed himself under the instruction of Sylvius and Fernel in the schools of Paris, attaining the degrees of Bachelor of Arts and Doctor of Medicine. For a time he occupied the chair of mathematics at the College of the Lombards, and in 1533 he was engaged in an active controversy with the Parisian Faculty of Medicine, the Dean and Faculty of Medicine having objected to the teaching of Judicial Astrology or Divination.[2] The case was carried into the Parliament of Paris, a body whose functions were judicial, not legislative, as in the English acceptation of the term, the result being a complicated and prolonged legal process which disenchanted Servetus with the French metropolis, and induced a change of residence.

We find Servetus first at Lyons in the capacity of proof-reader for the publishing house of Frellon Brothers, Mercière street, trading under the sign of Escu de Cologne. We find him later at Avignon. Thence he returned to Lyons, and finally established himself at Charlieu, where he practised his profession for three years. At the end of that time he returned to Lyons, where, meeting Pierre Palmier, with whom he had come into contact during his Parisian days, he was urged by him to make his home in Vienne, and, acquiescing in the proposal, took up his residence in this historic city, at no great distance from the Archiepiscopal palace.

The frequent changes of place which mark the life of Servetus may be attributed in a measure to the migratory tendencies of the medieval student and scholar. They were features of the intellectual life of the age. Traces of this vagrant character may be discerned in the drama of the Elizabethan era (see Hamlet, II, 2, "as the indifferent children of the earth"; also, the "terrae filii" of Jonson's "Alchemist"). In Vienne he might have passed his life in tranquillity, absorbed in the study of his profession, together with the congenial pursuit of literature as embodied in the fadeless types transmitted from the antique world, or in the novel forms, then blooming into vigorous and artistic expression under the auspicious guidance of the spirit of the Renaissance. He might have become a Sir Thomas Browne in the sixteenth century, or have been one of that rare and elect circle which mingled with Montaigne and read in their early freshness the essays which touched the thought of all Europe, fashioning the phraseology of Bacon, and contributing in at least one notable instance to the marvellous range and affluence of Shakespearean characterization. Yet no such propitious fate was in reserve for the young physician. The demon of theological controversy had entered in and assumed an inalienable possession. He had assailed the vital strong-

[2] Duboulay: History of the University of Paris, Vol. VI; also, account of this Academic Trial in Osler's Article on *Servetus*. Johns Hopkins Hospital Bulletin, January, 1910.

hold of the orthodox creed, and sooner or later the one issue was inevitable. Every opportunity that presented itself for the assertion of his heretical teachings was availed of with eagerness. He made frequent visits to Lyons and in 1543, while in that city, he assumed charge of a folio edition of the Bible published by Hughes de la Poite, the preface to which, written by himself, contained an exposition of his views, with marginal notes which were regarded by Calvin as not merely irreverent, but as actually blasphemous in character. Servetus again assumed the local name, Villanovanus, and Calvin mentions that he received 500 livres from the publishers for the work. (Abbé d'Artigny, Memoirs, pp. 65-66.) Calvin, who had known Servetus during his life in Paris, where they were both students, corresponded with him under the pseudonym of Charles Desparville, through the agency of the publisher, John Frellon. Servetus, who was not unknown in Vienne by his designation of Villanovanus, incurred not only the resentment and disapproval, but the implacable hostility of the Swiss reformer, whose creed he had assailed at a vital point in language almost unqualified and untempered in its nature. The correspondence came to a close in 1548, and Servetus addressed himself to the preparation of the work which assured his tragical fate at Champel.

To this book, known as "Christianismi Restitutio," he devoted four years and it appeared on January 3, 1553, with no indication or suggestion of either author or publisher. The book having been declined by a Basle publisher (Marrinus, by name), Servetus entrusted it to Balthazar Amollet of Vienne and to Guillaume Guérault, his brother-in-law, manager of the firm. In this epoch-making work, Servetus presents and defends his ideal religion, tracing back to the traditions of the primitive Christian age, in whose life the historic imagination reveals a unity and harmony which was in large measure the creation of its own genius. Though lacking in definiteness of language and clearness of exposition, it may be regarded as the first well-defined attempt, at least in modern times, to enunciate the principles of the pantheistic philosophy, or the doctrine of a supreme being or intelligence pervading all nature, yet impersonal in essence and in character. Emil Saisset justly assigns Servetus a place among the foremost precursors of such later oracles of the Pantheistic creed as Spinoza, Schleiermacher and Strauss. In this notable work there is revealed, despite its occasional vagueness of language and its fantasies, a conception of historic method upon which, as its basis, all the scientific achievement of a later age rests, though it was hardly even dimly descried by the explorers and researchers of the sixteenth century. From his day of dawn, it may be clearly assumed that he had been devotedly

> **"Nourishing a youth sublime,**
> **With the fairy tales of science,**
> **And the long result of time."**

The fifth book of "Christianismi Restitutio" contains a passage in reference to the circulation of the blood, in which he announces a discovery that must assure his rank in the foremost files of scientific investigators. "La vie médicale" (August-September, 1905) has the following comment upon this incident, forever memorable in the annals of medicine: "The first savant who saw the defects of Galen's theory was the Spaniard, Michael Servetus, who in his "Christianismi Restitutio" denied the permeability of the septum and affirmed that the blood of the right ventricle goes to the lungs where, after becoming red, it passes from the pulmonary artery into the vein of the same name." In this way, if the discovery of the greater circulation can be justly claimed by the English physiologist, William Harvey, 1615 being the date of its first announcement, and 1628 the time of its matured development, the discovery of the minor circulation must assuredly be attributed to Michael Servetus. Yet so late as 1669 the discovery of Servetus was ascribed to Lower (See R. Tigerstedt: Zur Geschichte des Kleinen Kreislaufs, Ergebnisse d. Physiol., Jahrg. II, p. 533), who quotes Cheneaux and M. Roth as proving that Matheus Realdus Columbus discovered the lesser circulation and that Servetus never pursued the study of anatomy except for a short time at Paris under the guidance of Gunther.

At this point we introduce an English translation of that portion of the "Christianismi Restitutio" in which the views of Servetus in regard to the circulation are explicitly set forth:

In order properly to understand this condition of things it becomes necessary to know beforehand the substantial generation of the life spirit itself, which is composed of the inspired air and finest blood, nourished by the same (Genes. 2, 7). This life spirit has its origin in the left chamber of the heart, the lungs especially assisting in its generation. It is a delicate spirit breath, produced by the force of warmth, of clear (flavo) color, burning force and to a certain extent composed of a transparent foam formed out of pure blood and containing in its substance water, air and fire. It is generated by the admixture of the inspired air and the thinned blood furnished by the right chamber of the heart to the left. *This, however, does not take place through the middle wall of the heart, as has been hitherto supposed,*[3] but by an highly intricate mechanism the finely divided blood is conveyed by *the right chamber of the heart by a devious route through the lungs.*[4] *The lungs prepare it for use by clarifying it* and pass it *from the arterial vein into the venous artery.*[5] It is thus mixed with *the inspired air* in the venous artery itself and by expiration is again cleansed from soot (a fuligine).[6] Finally the whole mixture is drawn through diastole, serving (if I may be permitted to use the expression) as a suitable household utensil for the life-spirit.

That this preparation and assimilation takes place in the lungs is manifest by the extensive union and anastomosis of the arterial vein with the venous artery of the lung. This is confirmed by the striking size of the arterial vein, which could not have reached such dimensions and have sent the blood from the heart into the lungs with such force by its own nutritive power, nor could the heart serve the lungs in a like manner, especially since in the

[3] Ut vulgo creditus.

[4] The honor of this discovery of 1553 was credited to Lower in 1669.

[5] Namely, in its origin in the lungs, as will be seen later. Furthermore, that arteria venosa means the veins of the lungs (pulmon. veins) and vena arteriosa refers to the arteries (pulmon. art.) of the same needs no further explanation.

[6] A fuligine (from soot). This may be regarded as a purely orthological difficulty, in that the word *fuligo* formerly had a different meaning (J. C. H.).

embryo the lungs receive their nourishment from other sources. In that those membranes, or valves of the heart (in membranulos illos seu valvulas cordis) are not opened until the time of birth, as Galen has taught. For this reason the blood is poured out so profusely from the heart at that time to serve another purpose.

The lungs also send to the heart not only mere air, but such as is mixed with blood through the venous artery. The admixture therefore takes place in the lungs, not in the heart. There is not room enough in the right side of the heart to accomplish such great and thorough admixture as to render the blood clear red. Finally, the middle wall, which dispenses with vessels and other adjuncts, is not adapted for transmission and distribution, although a portion may transpire.[7] In the same complicated manner as occurs in the liver, where transmission takes place from the portal vein to the vena cava (a vena portæ ad venam cavam) on the part of the blood, so also happens in the lungs the transfer from the arterial vein to the venous artery on the part of the life spirit.[8] If one compares this with what Galen describes in Books 6 and 7 on the function of these parts, he will grasp the truths therefor, although Galen himself did not understand this (ab ipso Galeno non animadversum).

This life spirit is then carried from the left side of the heart by degrees into the arteries of the entire body, which, as they become smaller and narrower and extend upward, it becomes more diffused, especially in the plexiform tissues at the base of the brain (in plexu retiformi), where it is transformed from mere life spirit into soul spirit, in so much as it here approaches the seat proper of the reasoning soul.

And now it is still more refined, elaborated and perfected by the finer vessels or capillary arteries (capillaribus arteriis) which are found in the arterial plexuses (in plexibus choroidibus) and which contain the intellect itself (ipsissimam mentem). These plexuses penetrate the innermost portions of the brain and form a lining to the interior cerebral chambers, entwining and enclosing those vessels up to their origin in the nerves so that they are rendered capable to the sense of touch and motion. These vessels, by wonderful arrangement so finely constructed, are in reality end arteries, and hollow the course or origin of the nerves through the coverings of the brain (ministerio menenguus). This is a new form of vessels.

As the merging of the veins and arteries in the lungs forms a new set of vessels composed of vein and artery, so also the union of the artery and nerve[9] forms a new sort of vessel from the arterial membrane to the cerebral lining, so much the more in that the covering of the brain retains its structure even into the nerves[9] (tunicas).

The entire first edition of this historic work was brought to Lyons. A part of it was placed on sale in the store of Pierre Merien, type-founder, near Notre Dame de Confort. Jean Frellon assumed charge of the rest. In virtue of the relations once existing between the author and Calvin, Frellon committed the fatal indiscretion of sending a copy of the newly issued treatise to the reformer. The contempt exhibited for himself and his writings, as well as the theological attitude revealed, aroused the implacable resentment of Calvin, and from that day the tragedy of Champel was a foregone result.

[7] Licet aliquid resudare possit: A courtesy to Galen.

[8] "Spirit" and "Life Spirit" would here correspond to oxygen and oxygenated blood.

[9] If the terms "Nervos" and "Nervis" were here replaced by venas and venis, it would afford a more intelligent understanding of the subject. Anastomosis of the arteries and veins was spoken of above, and even now the extremely fine vessels are termed "capillary-arteries."

The storm had been long gathering, for in February, 1546, Calvin had written to Farel, his co-reformer and devoted ally, that if his authority could still accomplish anything *he would never suffer him to leave there* (Geneva) *alive*—"vivum exire nunquam patiar."[10]

At this time Calvin had with him in Geneva a convert to his faith whose name was Guillaume Trie, and who was a native of Lyons. Trie maintained a systematic correspondence with Antoine Avneys, a relative of his, then living in Lyons, a loyal Catholic, who constantly and urgently appealed to Trie to return to his original belief. In February of this bodeful year (1553) Calvin requested Trie to write in his behalf to his kinsman a letter in which Servetus was described as one of the most dangerous of heretics, whether contemplated from the Catholic or Protestant point of view. The following copious extract will illustrate the character of the correspondence, and every utterance reveals the agency of the Swiss reformer:

With regard to doctrine and religion, he writes, although we enjoy greater liberty than you, nevertheless it shall not be permitted that the name of God be blasphemed, and that doctrines and bad principles be disseminated without being suppressed, and I can cite a flagrant example against you since it it necessary: namely, that they support among you a heretic who merits to be burned, wherever he goes. When I say a heretic, I mean a man who will be condemned by the Catholics, as well as by us, or at least he ought to be. For, though we are different in many things, we have this in common, that in one essence of God alone there are three persons, and that the Father has begotten his Son, who is eternal wisdom, before the beginning of time, and that he has had his eternal virtue, which is his Holy Ghost. Now, when a man says that the Trinity in which we believe is a Cerberus and monster of Hell, and vomits forth every wickedness imaginable against every teaching of the Bible with regard to the birth of the Son of God, and derides vilely all that the divines have said concerning it, pray tell me what respect would you have for him? . . . . There is one, however, who will call Jesus Christ an idol, who will destroy all the foundations of faith, who will collect all the dreams of the ancient heretics, who will even condemn the baptism of infants, describing these as diabolical inventions; and this man will be held in favor by you and be approved as if he had been guilty of no wrong! Where is the zeal in which you exult? and where is the order of that beautiful hierarchy which you extol in such emphatic terms? The man that I am describing to you has been condemned by all the churches with which you are in accord. Yet you have even conceded him the privilege of publishing his books, so charged with blasphemies that I need make no further reference to them. The man I have portrayed is a Spaniard, by name Michael Servetus. At this time, however, he styles himself Villaneuve. His profession is that of a physician. For some time he made his home in Lyons; he now resides in Vienne, where the book I have in mind was printed by an obscure creature named Balthazar Arnollet, who established a foundry in that city. That I may not seem to speak without evidence and with positive knowledge, I send you the first page of the work as a specific proof. You profess to believe that books which inculcate any teaching save the pure simplicity of the Holy Scriptures are contaminating, and if they are in conflict with the divine word, they are not to be tolerated among you. Yet, notwithstanding, you are nourishing in your own city a poison whose aim is the effacing of the Holy Scriptures and of every teaching you have received from Christ.

[10] H. Tollin: Saint Vertunien De La Vau, Virchows Arch., 1885, CI, 360.

We have unfolded in this letter the first well-defined phase in the drama which attained its final stage in the autumn of this year (1553). The purpose of Calvin is foreshadowed with relentless clearness. The vision of the stake at Champel rises before the mental eye.

The Cardinal of Tournon, combining civil and ecclesiastical functions as Governor and Archbishop, had in his service at this time an inquisitor whom he had summoned from Rome, the monk Mathiew d'Ory (whose name is never recalled without a sensation of horror), who assumed the title of "Penitent of St. Siège," inquisitor in France and in Gaul. As Calvin had anticipated, the letter of Guillaume Trie and the pages from the work of Servetus were placed in his hands. With the assistance of Benoît Buatier, canon in the Church of Vienne, Archdeacon de la Tour, Camarier of St. Paul in Lyons, Vicar General of Monseigneur of Tournon, and his archbishopric in Lyons, they were rigidly scrutinized, and it was decided to report the result to the cardinal, who at the time was residing in a château at Roussillon. Buatier left Lyons March 13, 1553, and called upon him in order to advise him of the result of the investigation. Louis Arzellier, supreme vicar of the Archbishopric of Vienne, was summoned to the château, and after a prolonged conference, the two grand vicars were despatched to Vienne with a letter containing the instructions of the cardinal to Mr. Maugiron, who, after being informed explicitly in regard to the intentions of the cardinal, sent for Antoine de la Court, sheriff of the city, with a view to instituting legal proceedings against Servetus, who, in official papers connected with the trial, is always described as Michael de Villeneuve. On March 16 his home was searched, but there was nothing brought to light that implicated him, or created a suspicion of heretical teaching. The judges, impressed by the depositions made on the preceding evening before the official primate, Peyrollier, by the grand vicar and vibaille of Vienne, on the 17th sent for Guillaume Guérault, but were unable to elicit any information from him. The printers, upon being questioned separately, replied that among the books which they had printed for two years, there had been none in octavo. When the proceedings were concluded, the judges summoned to appear before them the printers, compositors and servants of Arnollet, together with their wives and servants. They were enjoined not to disclose anything that had occurred, or to make known any point in reference to which they had been cross-examined, under penalty of being regarded and punished as heretics. On the day following, March 18, Arnollet, having returned from a visit to Toulouse, was subjected to cross-examination, and made denials, the same in character as those of his brother-in-law, Guérault. The judges, in a session held at the house of the archbishop, decided that sufficient evidence had not been produced to justify or warrant the making of an arrest.

On March 19 the archbishop summoned Mathiew d'Ory, the inquisitor, to Vienne. D'Ory advised the judges that, in order to secure sufficient evidence to lead to the conviction of Michael de Villeneuve, his treatise "Christianismi Restitutio" should be examined in its complete form and not in fragments or in passages detached from their context. To render this practicable, it was decided that the Sieur Arneys should communicate with his relative in Geneva and obtain through his agency a copy of the treatise instead of specimens or illustrations which were not sufficient to exhibit its genuine character. This measure being determined upon the inquisitor returned to Lyons and dictated the letter which Arneys was to transmit to Guillaume Trie. Through his confidential agent Calvin replied March 26, sending a greater variety of documentary evidence than was requisite to assure the conviction of Servetus, as, for example, two dozen letters written by him during his controversy with the reformer in preceding years. The proof thus furnished was supplemented by another letter, received on March 31.

On April 4 the cardinal of Tournon, the archbishop of Vienne, Pierre Palmier, the two grand vicars, the inquisitor, several ecclesiastics and doctors of divinity assembled at the Roussillon château. The documents last received from Geneva, that is, the two letters of Guillaume Trie, a copy of "Christianismi Restitutio" with marginal notes in the handwriting of Servetus, and more than 20 letters which he had addressed to Calvin, were subjected to examination. The charge of heresy was established beyond all question. Servetus was convicted upon his own testimony. By unanimous agreement the cardinal and archbishop proceeded to arrest Michael de Villeneuve, physician, and Balthazar Arnollet, publisher, and to require of them an account of their faith, as well as an answer to the charges and information laid against them.

When dinner had been finished the archbishop returned to Vienne in company with his grand vicar, and communicated to the vice-bailiff the purpose of the cardinal. In order to prevent a discovery of the plan, it was determined that Servetus and Arnollet should be arrested simultaneously and consigned to different prisons. About 6 o'clock the grand vicar approached the house of Arnollet and directed him to produce the New Testament which he had printed. The publisher appeared and was committed to the prison of the archbishopric. At the very same time the vice-bailiff (or his deputies) proceeded to the home of Maugiron, whom Servetus was attending in his professional capacity, and, advising him that there were several sick and wounded prisoners in the Royal Palace, requested him to come to their relief. Servetus replied that his duty as a physician, as well as his desire to minister to suffering, induced him to comply. They then proceeded to the Royal Prison, and while Servetus was devoting himself to his patients, the deputy despatched a messenger to the grand vicar requesting his presence. As soon as he arrived, Servetus was notified that certain charges and information, communicated to the Seigneur Cardinal de Tournon, had been laid against him, and that he was to remain a prisoner in the palace until the charges were answered, or different instructions were received in reference to his case. He was then committed to Antoine Bouin, provost and jailer, with a special injunction to guard him rigidly, at the same time according him the consideration due to his rank and his professional character. He was allowed to retain his servant, Benoît Perrin, aged 15,

who had been five years in his employ. (Memoirs, Abbé d'Artigny, p. 100.)

On the next day, April 5, the inquisitor, Mathiew d'Ory, came to assume charge of the proceedings involved in the examination of Servetus. The examination continued on the 6th, and soon after Servetus sent Perrin to the monastery of St. Pierre to ask for 1500 francs ($300) which was due him at the Côte St. André, and the grand prieur, to whom the request had been presented, produced and paid him the amount. Almost immediately afterward the inquisitor prohibited Servetus from conversing with anyone save by special permission, and enjoined the severest vigilance upon the jailer to whose charge he had been committed. This rigorous treatment was an involuntary tribute to the generous and philanthropic spirit which was characteristic of Servetus and had won him troops of friends in every sphere of society. He had healed the vice-bailiff's only daughter of a dangerous malady; he had also restored the son of the governor, Louis de Maugiron, and during the desolating plague of 1543 he had devoted himself to the relief of the stricken. Naturally, the inquisitor feared that he might escape, and the result proved that his apprehensions were not unfounded.

On April 7 Servetus arose at 4 a. m. and asked the jailer, who was directing some work in his vineyard, for the use of the garden key. Mr. Bouin did not suspect his purpose, as Servetus very adroitly had robed himself in his night-cap and dressing-gown, which concealed his accustomed clothing, his hat being hidden by the gown. He complied with his request, gave him the key, and proceeded with his superintendence of the workmen. As soon as they had advanced a sufficient distance from him to justify his taking such a bold and daring measure, Servetus left his black velvet bonnet and furred dressing-gown at the base of a tree, leaped from the terrace of the garden to the roof below, and from thence to the yard of the palace. He reached the gate of the bridge which spans the Rhone, an ancient landmark of the Roman occupation of Gaul, extending from Pichat Square to the tower of Philip VI of Valois, opposite St. Colombe, and hastened in the direction of Givois and Lyons, as was testified by a country girl whom he met on his route. Fortunately for Servetus, she was not examined until three days after she had encountered him. More than two hours passed before his escape was discovered. The wife of the jailer was the first to be informed, and in her despair, "she gave way to every form of wild and frenzied action, such as tearing the hair, beating her servants, her children, the prisoners whom she chanced to meet, even incurring the danger of running over the adjoining roofs in her frantic eagerness to recapture the fugitive. She had been suddenly transformed into a maniac."

Every possible effort was made by those in authority to recapture Servetus. The gates of the city were closed and guarded during the night of that day and the day following. After proclamation by the trumpet a thorough and rigid search was made of all houses, including those in St. Colombe. The magistrates of Lyons and other neighboring cities in which it was possible that Servetus might have taken refuge were at once notified. They even investigated the financial condition of the escaped prisoner by application to the banks of Vienne; an inventory of his papers, furniture, and all his personal effects were placed in the hands of the local authorities (Abbé d'Artigny, Memoirs, p. 112). On the 2d of May the inquisitor brought to light, in a remote and lonely house, the two presses which had been used for the printing of "Christianismi Restitutio," and ascertained from Thomas Straton, one of the employees, that he had forwarded on January 13, by order of Servetus, five packages of books to Pierre Merrin, a type-founder, living in Lyons near Notre Dame de Confort. The five packages were returned to Vienne on the 10th of May. The inquisitor prepared a synopsis of the principal errors contained in the work, with a view to emphasizing the effect of his censure or judgment by commenting upon passages detached or isolated from their context, an effective mode of distorting their meaning and perverting the teaching of the author. By the coming of June, the investigation had been completed and the following verdict was formally rendered, the text being literally reproduced from the archives of the old archbishopric in Vienne:

We, having seen the documents of said heresies, also the letters and writings of said Villeneuve, addressed to Mr. John Calvin, preacher, at Geneva, and avowed by the said Villeneuve (the said Villeneuve admitting the fact), his answers, confessions and denials, the answers and other procedures, Balthazar, the printer, agreeing, certain packages and printed books under the title "Christianismi Restitutio," witnesses being examined to ascertain if the said Villeneuve had written and printed the said book at his expense, the reports of D. D.'s and other notable persons concerning the errors contained in the said book and letters, which errors and heresies are, moreover, made evident when read, documents concerning escapes from prisons, and proceedings to arrest the said Villeneuve; the collected testimony, the final conclusions of the attorney of the King Dauphin, and everything considered, we have declared that the said faults have been duly obtained, in profit of which we have estopped and estop the said Villeneuve from every plea and defense; we have declared and do declare him guilty of and convicted for the offenses and crimes attributed to him, for reparation of which we have condemned him and condemn him to pay a fine of one thousand livres currency to the King Dauphin; and to be, immediately after his arrest, taken on a tumbril with his books the next day from the market of the Royal Gate through the most populous and frequented streets and places as far as the market of this city, and then to the place called Chanève, and now St. Martin Square, there to be burned alive over a slow fire until his body is burned to ashes. Nevertheless, this sentence shall be executed upon his effigy, and with it shall burn the said books.

And since we have sentenced him and sentence him to pay expenses and costs, of which we reserve the assessment, we declare all his property confiscated for the benefit of the heir, the said costs and damages claimed on this property being first paid. De la Court, bailiff and Royal Judge, Giotel, Cavier, Rutod..... .....assessors.

The said sentence being delivered in open court before the said attorney of the King, we, the aforesaid, sitting in court in the Royal Palace in Vienne, the 17th of June, 1553, in the presence of Philbert Gollin.....and several other practitioners of Vienne, witnessing with the undersigned clerk of the Court, Chasalis.

On the same day, June 17, the sentence was executed in effigy, as is attested by the official report of Francis Barode,

who carried it into effect, his statement having been prepared by the clerk of the court.

Our narrative now hastens to its climax. Servetus had escaped from the jaws of the Roman lion merely to be committed to the tender mercies of the relentless autocrat who dominated the civil as well as the ecclesiastical polity of Geneva. He had fled from Scylla only to be cast upon Charybdis. It may be assumed without intolerance of spirit or extravagance of language that the last state was at least not better than the first. He was arrested in Geneva on the 13th of August, while in attendance upon a religious service, and once in the hands of Calvin, the martyr's crown was a foregone result. His apparent purpose in passing through Geneva was to effect a return into Italy which, it may be supposed, still retained for him the charm that marked his early years (1523-1530) in the service of Charles V. There, too, he had absorbed those heterodox conceptions of the Trinity which heralded the way to the autumnal tragedy on the slopes of Champel.

The trial of Servetus, as conducted under the all-potent direction of Calvin, was a far more complex and prolonged judicial process than might be inferred from the ordinary accounts which have been transmitted to later ages. It extended from August 22 unto October 25, when sentence of death was pronounced against him. Nor was the autocrat and theocrat of Geneva suffered to bring his victim to the stake without vehement resistance from the party of the Libertines under the leadership of Perrin, which withstood with tenacious energy the intolerant sway and all-pervasive tyranny of Calvin, and embodied in its ranks the finest flowers of Genevan social culture, as well as the purest expression of its chivalric ideals. Encouraged and stimulated by the co-operation of so powerful a party, Servetus, who, in the earlier stages of the trial had borne himself with dignity and moderation, assumed a violent and denunciatory attitude with regard to his invincible antagonist. Yet it availed not, and despite all the efforts of Perrin, the sentence of death at the stake, pronounced on October 25, was carried into effect at 11 a. m. on the 27th.

The story of the long-drawn agony of Servetus in the flames, the rescue of his book, condemned to perish with him, his refusal to disavow his belief, even in the eye of death, his invocation with his fast fleeting breath of the mercy and compassion of Christ, have all been wrought into the historic consciousness of the ages that came after.

> "He nothing common did, or mean,
> Upon that memorable scene,
> Nor called the gods with vulgar spite
> To vindicate his helpless right."

Yet in no sense can the discoverer of the lesser circulation assume rank among the martyrs to the spirit of scientific discovery. His physiological teaching seems to have been responsible for no part of the combined movement, Catholic and Protestant, that brought him to the stake. The demon of theological speculation had entered his soul and the demon of theological intolerance pursued him with its unique and unresting malignity until there remained no trace of Servetus in the world, save scattered ashes, a name from that time famous, and a mournful memory. In assailing the doctrine of the Trinity inculcated with invincible devotion by the whole Christian communion, he had left himself no sanctuary or asylum; his attitude was one of hopeless, irreclaimable isolation. To impugn the orthodox creed in this special phase of belief constituted an offence against both the civil and ecclesiastical code which involved grave consequences and placed the offender in a category not unlike that assigned to an anarchist or a dynamiter as contemplated from the viewpoint of our modern civilization. Sadducees and Pharisees, the society of Jesuits and the theocratic forces marshalled by Calvin, made common cause against their common enemy. The Catholics burned Servetus in effigy at Vienne; Calvin burned him in reality at Geneva. One was the preluding rehearsal, the other the ghastly tragedy.

In addition to his heretical attitude with reference to the Trinity, Servetus had been imbued with the teachings of the Anabaptists; he strenuously repudiated the doctrine of infant baptism and was involved in the odium attaching to this widespread sect whose name was almost a symbol for licentiousness and disorder. Against the combined forces of Trinitarian orthodoxy, the attempts of the Libertines to pluck Servetus from the grasp of Calvin recoiled as vain and impotent.

A determining element in sealing the doom of Servetus was the critical condition of the Protestant reformation during the years contemporary with the final period of his activity, or, to express it in other terms, the period which marked the middle of the sixteenth century. The outlook for Protestantism was dreary, it might be even hopeless. The Marian, or Roman Catholic, reaction in England dates from 1553; the Society of Jesus was undoing the work of the Reformers with seemingly resistless energy; Geneva was confronted on the one side by the Valois monarchy; to the North was the empire of Charles V; and Luther had been dead for seven years. The isolation of Calvin was almost complete; "a pillar steadfast in the storm," the last refuge and stronghold of the cause of Protestantism. The escape of Servetus would have implied a fatal weakness on the part of Calvin and his colleagues. The issue was not personal, not local—it was all-embracing in character, and in the result was involved the very life of the Protestant reformation.

That his scientific or physiological teachings were not introduced as an element of antagonism to Servetus reveals one of the most suggestive phases of his strangely dramatic and almost unique career. The question seems never to have been presented save as containing another form of heresy. The theological aspect of the controversy was the exclusive issue, for the oracle of Geneva, Calvin, despite his austerity of nature and inflexibly dogmatic temperament, was endowed with a sense of literary and scholarly appreciation that has won for him no inconspicuous rank in the records of linguistic evolution during the sixteenth century. He was not indifferent to the charm of science or hostile to its development. In marked contrast to the spirit which asserted itself at the time that William Harvey first announced his discovery (1615), he would not have condemned Servetus for his theory of the

lesser circulation. Harvey incurred financial loss by the promulgation of his novel views, and it is said that they were not accepted by any physician beyond the age of 40. When they were given to the world in their matured form (1628) they appear to have gained favorable regard by slow degrees, and in 1633, when Giles Fletcher published his "Purple Island," the "thousand brooks," representing veins and arteries, were described in accordance with the ancient doctrine, in apparent ignorance of the discovery of Harvey.

The charge of plagiarism which has been suggested with regard to the scientific teaching of Servetus[11] need not be dwelt upon here further than to say that it is groundless. His mind seems to have been marked by rare originality and creative power. A vein of mysticism and a touch of poetry reveal their influence in his style; the sensibility of his Spanish nature at times shines through the dialectic dreams and reveries of the work that attained its logical climax at the spot now designated by the monumental granite block (dedicated November 1, 1903) which constitutes the Expiatory Monument.

The strongly developed anti-dogmatic tendency of Servetus suggests many parallels and analogies in varying ages and under diverse historic conditions. Perhaps no one of them is presented in stronger light than Archbishop Whateley, whose attitude in reference to the dogmas formulated by theologians exhibits a striking resemblance to that enunciated by the antagonist of the Swiss reformer. The execution of Servetus was regarded by the contemporary theological world as a vindication of truth and a triumph of righteousness. The entire Protestant communion approved the deed; the gentle Melanchthon was especially emphatic in his expression of concurrence. In no sense did Calvin regret or repent his action. On the contrary, he acquired new strength and influence as the champion and vindicator of the Reformation against heresy. The Church of Rome could not longer exercise the sole prerogative of inflicting vengeance upon the enemies of the Gospel. Scandalized, as Gibbon naturally was more than two centuries later, by the burning of Servetus, it none the less remains an invincible truth that Calvin concretely represented the dominant religious ideals and the purest political aspirations attained by his own era.

It is a notable historical fact that the penalty of death for denying the doctrine of the Trinity was inflicted in Protestant England during the reign of James I (1611),[12] long after Calvin and Servetus had passed to their account, and that while the statutes which defined its character became gradually void and inoperative with the growth of a tolerant spirit, they were not formally repealed until a time that is strangely and suggestively near to our own era, with its tendency toward anti-dogmatism, if not toward indifferentism and agnosticism—the negation of all definite or positive belief.

The Expiatory Monument, erected by the combined efforts of the Reformed Churches of France and Switzerland and dedicated with impressive ceremonies Sunday, November 1, 1903, occupies a position perhaps unique in the records of the Christian religion, if not in the annals of the world. Monuments have been reared by societies or representatives of ecclesiastical organizations, in order to embody in abiding form their expression of repentance and contrition, elicited by the consciousness of grievous wrong or atrocious persecution inflicted upon opposing faiths, or upon antagonizing systems and beliefs in the sphere of philosophy or in the province of political polemicism. The long-deferred confession came from the successors or representatives of the creeds which were involved in the act in its original intolerance. The attitude of the monument at Champel is one of complete isolation. It has no prototype or counterpart in all records. It was created by the co-operative efforts of those whose religious ancestors had wrought the deed of shame, by loyal successors of Calvin devotedly attached to the cardinal teachings of the Reformation of which he was the vital force, and which, in its critical moments, he plucked almost from the grasp of despair. The granite block is not merely distinguished from every other monument of which the ages hold record, it stands aloof even from the other monuments erected to perpetuate the genius and the achievements of Servetus. By no means the least of the claims to honor and renown which are the inalienable prerogative of the medical profession is the simple reminder that this phenomenal tribute of the modern spirit had its inspiration and its outcome in the life and labors of a physician. The motto of the city of Geneva, "Post Tenebras Lux," seems to reflect an undreamed-of radiance of meaning, as we contemplate the massive granite hard by the Church of St. Peter, in which Calvin was accustomed to preach and where his memory is still held in reverence, perhaps more discerning and rational in its nature, as the world with resistless gravitation sweeps into the younger day.

"Doctrina sed vim promovet insitam,
Rectique cultus pectora roborant;
Utcunque defecere mores,
Indecorant bene nata culpae."

[11] This matter has been thoroughly investigated by the author in his "History of the Circulation of the Blood—Contributions of the Italian Anatomists, Psychologists, etc.," Johns Hopkins Bull., 1905, May, Vol. 16.

[12] The "Atheism" of Sir Walter Raleigh and the "Arianism" of John Milton and Sir Isaac Newton are suggestive to the student of science as well as to the student of literature.

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THE PSYCHOSES OF THE HIGH-IMBECILE.

By HENRY J. BERKLEY, M. D., D. Sc., Baltimore.

Generalizing, it is well to remember that the high-imbecile from the cradle onward develops slowly; that he is behind the normal child in learning to walk and to talk; that in attention as well as imitation he is backward, and that when childhood begins and school life opens he shows up as a dullard or one-sided individual. In his habits he is negligent and untidy, and is often the sport of better endowed companions, an item that has a bearing on the whole of his future life. In his class-life he is in constant conflict with his teachers, to whom he is a despair.

The final scholastic attainments are, as a rule, a superficial knowledge of reading and writing. Spoken language, on the other hand, is often voluble, though it will be found on examination that the vocabulary is limited, and that scanty ideas are submerged in a torrent of oft-times meaningless words. Few are at all proficient in arithmetic, even those who have had a fair opportunity of obtaining a good education; with the automatic indrilling of the multiplication table their ability ends; subtraction, division and compound multiplication remaining an unfathomable riddle. Many fluent in language cannot tell the hour by the clock, and in abstract deduction of a simple problem they show no reasoning ability.

When the age of adolescence is attained the rise of the sexual instincts, as well as altered conditions—the increased personal liberty and freedom from restraints formerly imposed by parents and guardians—seem to aggravate all their propensities for evil; excesses of all kinds are now indulged in.

At this period lues is often acquired and plays an important part in their subsequent mental degradation, but, in the majority, inebriety has an even more prominent rôle in this respect. Few are there among the high-imbeciles that do not show its after-effects when psychoses develop, as is evidenced by the hallucinations and the delusions of persecutory cast.

In the list of delinquencies thefts are frequent, to obtain the necessities for future pleasures; rapes are usual when money or means are lacking to attract the weaker sex; vagabondage and mendicancy are common, so that children of respectable parentage are found harboring with thieves and prostitutes to their own detriment as well as to the scandal of the community in which they live.

Not infrequently, after a course of dissipation, the defective inherited protoplasm comes to the succor of the family pride. A few months of excesses and the hereditary weakling becomes passive, inert and unable to take care of himself; in other words, he becomes demented, and seeks the sheltering walls of an institution, to be cared for to the end of his days.

There seems to be some law of premature senescence descending upon members of the imbecile class about the age of adolescence that renders a future development of viciousness as well as licentiousness impossible—an impossibility perhaps due to some conflict between the correlation of the internal secretions. In any event, the mental development comes to a stand-still, with eventual retrocession; it may be after the lapse of only a few months. It should be remembered in this connection, as having a direct bearing upon the subject at issue, that the age of puberty and adolescence is the most trying period in the evolution of the higher cerebral association fibers, rapid growth of the body occurring with advancing maturity of the sexual system, and in these individuals the cytoplasm necessary for successful development is both deficient and defective. Hence a rapid decline of the neural vitality and a terminating mental reduction.

Alcoholism, syphilis, the excessive use of tobacco, late hours, as well as over-drain upon the sexual organs, all play a decided and important part in the immediate mental downfall of the defectives. Few examples of hallucinations are found without some antecedent history of alcoholic misuse.

The stigmata of degeneration in the high-imbecile class are much less frequent and pronounced than in the lower types; the physiognomy is less explicit in its tale of intellectual barrenness. In fact, many of the so-called moral, emotional or impulsive cases are sufficiently high in the intellectual scale not to portray to the untrained mind their actual degree of weak-mindedness and, accordingly, among the masses, they pass for normal individuals. It has been said that clothes make the man and certainly a well-groomed individual offers less to the eye that is suggestive of mental defect than those that are unkempt and untidy. But, by examination with the Binet method, or with the simpler arithmetical tests, together with questions as to judgment and insight, a fair knowledge of the degree of mental endowment may be ascertained within a few minutes, and the results are often surprising, showing as they do an incompetence that was entirely unsuspected from the surface.

The psychoses of the moron class are extremely varied, complicated, interesting, and have not been sufficiently studied, mainly because the majority of mental workers have not been taught to recognize the imbecile in his highest development, when he stands nearest to the normal man; and although they recognize that in certain cases running the course of an atypical catatonia, hebephrenia or early dementia the patients are of sub-normal mental grade, they lay but little stress upon this fact.

Grading carefully from the lower types of imbecility to the moron group, the last showing but few physical and still fewer gross psychical defects, we find that a high percentage of the permanent inhabitants of institutions (excluding seniles and paretics) have a defect in their mental gearing of the most varied degree and characteristics, with which is coupled a psychosis.

Naturally, the insanities of the high-imbecile fall among recognized types of adolescent psychoses, but at the same time and in endless variety they depart from classical cases of these maladies in symptomatology and duration.

Tabulated, we find cases in the clinic resembling:

(1) The dementia præcox group.
  Catatonia.
  Hebephrenia.
  Paranoid forms.
(2) The alternating insanities.
  Periodic and circular forms, with pathological exaltation and depression.
  Stuporous states, either simple or alternating with motor excitement.
(3) The dementia group.
  Dementias progressive in character, without depression or exaltation of any duration.
(4) Cases with especial disturbance of hearing, sight and gustation.
  Acute and chronic hallucinosis.
(5) Cases that are especially characterized by the presence of false ideas.
  Acute and chronic delusional states.
(6) Cases whose principal feature is the occurrence of impulses or impellent acts of a pathological nature.
  Obsessions and pathological impulses.

But the course of the first two of the above divisions does not follow closely the cardinal types. Most notable in all of them is the tendency toward a quick dementia, which is final and often complete, but even to this rule there are certain exceptions, especially among individuals showing a simple motor excitement free from delusions and hallucinations.

Another difference lies in the short course of the malady in contrast to the longer duration in the typical cases of catatonia or periodic insanity. In the high-grade imbecile the psychoses end after a few days or weeks in a quick return to the former mental state or in an equally rapid mental reduction and passivity.

Furthermore, and as a cardinal point, the onset of the psychosis is more sudden and without the preliminaries of the catatonic or manic-depressive types; the attack is briefer, the return to former mentality more complete within a shorter space of time. In the absence of alcoholic abuse hallucinations are rare.

Returning to the above classification and simplifying it to a certain extent, we find:

(1) *Cases of Pathological Exaltation, with the Features of Short Course, Rapid Termination in a Dementia or Return to the Former Mental State.*—These forms of excitement are common, especially with adolescent youths and are uncomplicated by alternating depression or hypochrondriacal fancies; in fact, delusions themselves are infrequent or of the simplest character. The outbreak of the malady is characterized by a sudden onset, violent as well as extravagant tendencies, logorrhea with incoherence in the assemblage of ideas, also by a varying degree of intellectual confusion during the period of excitement, this passing sometimes into actual stupor, out of which the patient returns to his normal state. In this class, on the whole, the motor are more pronounced than the mental symptoms. The duration of the entire seizure is short, a few days, infrequently a few weeks, with restitution or dementia according to the strength of the inherited protoplasm. Attacks in those fairly endowed are liable to be repeated from time to time; occasionally a patient is seen that has had only one, though he may suffer at times from irritability not amounting to an actual psychosis.

(2) *States of Pathological Exaltation in Individuals of a Slightly Higher Mental Grade than the Preceding Class.*—With thought confusion are now mingled delusions of pronounced but varied character. Dependent upon abuse or non-abuse of alcohol their content varies from simple delusions of personality, surroundings, power, wealth, and above all, those that belong to a perverted egoism, to varied delusions of persecution, mainly attributed to persons with whom they have been in contact in their own household or at the work-shop. These false ideas are systematized to the extent that they do not vary greatly from day to day and may last for many weeks. Hallucinations even in moderate alcoholics (or cocaine habitués) are usual. Those of hearing are of a persecutory cast, unfriendly voices telling them that they are foul with syphilis; are no longer men; that their wives are unfaithful. Those of sight are also frequent with this class. They see figures or pictures moving in the trees. God or the devil appears and commands them to do certain acts. Hallucinations of being covered with creeping vermin, that burrow through their flesh, are also common. Gustatory deceptions are less frequent.

In the case of the majority of the individuals of this class one attack brings them to the asylum and, although they may recover to the extent of becoming quiet and manageable, the finer part of the faculties is blunted, and they are no longer capable of returning to their vocations or, unassisted, of attaining to any steady employment, though they may do fairly well under the guidance of another and stronger mind. Eventually they slowly descend in the mental scale or, after repeated attacks, become completely fatuous.

(3) *Cases that show a variation from the second type,* in so far that, after a period of moderate pathological hyperactivity, with delusions and frequently hallucinations, deep confusion begins, ending in stupor with catatonic rigidity, negativism, as well as resistance to passive extension of the extremities. The circulation is low, the heart's action feeble, the extremities cyanotic, and the vitality falls to a low ebb. Death occasionally occurs in this state of stupor, without any return to consciousness. In the depths of the lethargy the quivering eyelids are the only signs of life; the pupils are widely dilated, the face is pallid, while the respiration is slow and uncertain.

In the less severe cases partial restitution takes place within a period of two to four weeks, the victim no longer requiring to be tube-fed and being more energetic; but the delusions continue unabated, slowly to fade in the darkness of a dementia that is final.

(4) *Paranoid tendencies* are frequent with the high-imbecile. Alcoholism and masturbation are the foundation stones, in common with other agencies of a depressant nature. In the brain of the three-quarter wit, probably after a series of misfortunes, mainly owing to his incompetence or inattention to duties, there comes to be evolved the idea that the hand of mankind is against him; that he is being kept down by favor-

itism toward others and robbed of his proper deserts. The essential egotism of individuals of the moron class, deep-lying and always ready to take offense, when errors of omission or commission are corrected, renders them unduly sensitive to the "blows of unrequited fortune"; they sink more and more within their inner selves; introspection, with alcoholic excesses, soon lowers the mental vitality; false ideas that they are objects of persecution or sport by their fellow workmen arise; soon aural hallucinations are added to the delusions that they are the subjects of unwarranted hostility from their fellows; unfriendly voices assail them, coming from whence they do not know, as they reach them on the street or in the quietude of their own abodes. Soon attacks on employer or fellow-workmen supervene, the police interfere, and the gates of the asylum open.

After entering an institution the mental downfall is usually rapid. At first voluble with their complaints to the medical men or attendants of the institution, there is soon a withdrawal from association with other inmates and an intensification of the persecutory ideas, which is followed within a year by a deeper and yet deeper dementia, though this class rarely becomes so fatuous as those of the first divisions.

(5) *Cases Resembling the Alternating (Manic-Depressive) Insanities.*—From the narrow egotism of the moron class it may readily be imagined that examples of real depression are far less frequent than those of excitement and stupor, the true periodic cases standing on a higher plane of mental altitude. Like the states of excitement of the first and second classes, they show the same sudden beginning with few antecedent preliminaries, short course and ordinarily rapid termination. With the majority that fall under this category, the stage of excitement is marked by a deeper clouding and confusion than is usual with the typical manic depressives; ideation is shallower and delusional ideas more pronounced. Motor agitation is sometimes well marked; at other times trivial. The periods of depression show energy rather than delusional depression, while the mental level of the entire psychosis impresses one as being more grave as well as more irremediable than in pure alternating examples.

(6) *Stuporous states*—not the occasional stuporous conditions of the periodic or of the catatonic, but of a character quite apart from these, and manifesting but little of their symptomatology except for the more prominent element. In the moron instances of simple stupor, except with women at the time of menstrual periods, are rare. With little disturbance of the vital functions and still less of delusional or hallucinatory implication, these individuals for a short time become irritable, restless, or as they express it, "nervous"; then suddenly they pass into a deep passive sleep, out of which nothing in the way of varied stimuli can arouse them. They require to be tube-fed and in every way looked after. After the lapse of from ten days to two weeks they suddenly, often in the early hours of the morning, come out of the realms of night into those of day. During this state of total anergy there are no muscular movements, no negativism, nothing approaching a cataleptic condition; only passivity. The pupils are widely dilated, the pulse slowed, the respiration tranquil but shallow. The temperature is usually sub-normal. The tendency is to recover after a time, but, contrary to what happens in the preceding varieties, the malady is not customarily followed by a mental decline, except when the attacks have been repeated over and over again. Questions, after recovery, as to their recollection during the phase of stupor, ordinarily elicit but little information. Some refer to it as a prolonged uncertain dream; others have no distinct remembrance at all.

(7) *Progressive Dementia Without Active Motor or Psychic Symptoms.*—Not a great many cases coming under this category have fallen under my notice. The majority were not high in the mental scale, and some had the brand-marks of an inherited syphilis. Spinal fluid tests were frequently positive.

In the earlier stages there comes a time of ill-defined nervous agitation without definite delusions or hallucinations, after which the subjects slowly dement without further active symptoms. Not a few examples show the evidences of a chronic arteritis, sometimes luetic, sometimes of other types, and as definite histories are frequently lacking, it may be presumed that some have suffered from typhoid or other infectious fevers which, together with the after-effects of the accompanying irritant toxin, has induced a chronic state of nutritional defect leading up to the psychosis. The general bad effects of licentiousness in this class have already been considered.

With a number of ill-balanced children, who have been forced to undertake a school education ill-suited to their strength and mental endowments, the continued strain of years of effort results at the time of adolescence in a mental decrepitude from which after-treatment is powerless to rescue them, and they descend slowly to the plane of the dement.

In the first stages there is a period of ill-defined restlessness with depression, passive in nature, but without delusions, hallucinations or motor excitement. Soon this restlessness passes away and is succeeded by a dull apathy, the victims taking no interest in anything about them, remaining dull-eyed to questions or stimuli of varied nature and not even reactive to loud noises or pin-pricks. All day long they sit passive on the benches with bowed head and drooping shoulders, eyes directed to the ground, unseeing, with hands livid and oozing sweat and so remain for months until removed by a pneumococcus or colon bacillus infection.

In addition to syphilis and infectious diseases, it may possibly be that a lack of correlation between the internal secretions is again a principal factor in this passive dementia. Not a few have deficient thyroids and occasionally one may feel in the lobes of these organs little hard nodules that are abnormal.

(8) *Chronic states of delusion and hallucination* are mainly attributable to the after-effects of drugs and especially of alcohol. Auditory hallucinations are of more importance than visual ones, as they exert a deeper impression upon the sufferer, being but reflexions of his abnormal thoughts, and accordingly are not so readily corrected. These false ideas and sense fallacies are in a measure permanent, fixed, in a crude way systematized, have a persecutory cast and materially influence the lives of individuals, becoming to them the most

prominent feature of their daily life, as well as influencing all their actions. Eventually they lead up to attacks upon others or to suicidal attempts. Insight and judgment are seriously affected and at last there begins a noticeable degree of dementia, which deepens as the months advance, the sensory fallacies becoming less and less prominent until eventually lost in the mental clouding.

We especially desire to call attention in this paper to the fact that the high-imbecile is far more prone to the psychoses than a man of higher mental development; that practically all forms of simple and complex mental disorders are to be found among them, though a number are represented in simplified form; that the pernicious action of alcohol in particular, as well as of other drugs, although in less frequency, is much more marked in them than in normal man and is, in fact, the corner-stone of the vast majority of their hallucinations and delusions; finally, that few make a complete recovery from any of the forms of psychosis above enumerated, a terminal dementia of quick onset being the rule.

One addendum we desire to make to this article before closing. It is an inflexible law of Nature that like can only produce like. The high-imbecile reproduces his kind and, unrestrained by ethical laws as well as by care of the future, in ever-increasing numbers; the progeny to be an increasing burden upon the tax-paying community, as well as a sore strain upon the upkeeping of the law. If we leave this portion of the population to increase unrestrictedly and at an unnatural rate in proportion to the total increase of the population, one result is inevitable: they will eventually overwhelm by sheer numbers the producing people and the race will then sink to a low level.

I am reminded of a short story read some years ago, depicting the earth a thousand years hence. According to the author some fearful cataclysm had everwhelmed the entire world, leaving but few of its folk, and these soon degenerated. It is true they multiplied in numbers, but they further descended in the mental scale to below, far below, the rapine beasts of the field. Fire they knew not; war and slaughter were their only arts; while cannibalism was prevalent. Their only science was to destroy.

The only solution of the problem of the high-imbecile is sterilization; a general law affecting all the states should be enacted compelling the castration or spaying in all educational institutions or asylums for the insane or defectives of those who are capable of reproducing their kind. Many physicians are opposed to such a law, mainly on the ground that it might produce an increase of venereal diseases, but these considerations are of minimal importance compared with the general deterioration of the entire race. *Salus populi suprema est lex.*

A DERMOID CYST SHOWING UNUSUAL FEATURES.

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(*From the Dermatological Clinic of The Johns Hopkins Hospital Dispensary.*)

CASE REPORT.

J. C. N., a negro, aged 40 years, presented himself for treatment at the Dermatological Clinic of The Johns Hopkins Dispensary in March, 1913.

Just to the left of the center of the forehead was a small round tumor about 7 mm. in diameter, which clinically presented all the features of an ordinary sebaceous cyst. It had been present four years and showed the usual comedo-like opening. It was smooth, freely movable over the deeper structures, and had shown no recent rapid increase in size. Some months previous to the appearance of the tumor, a long lanugo hair had developed at the point, which later was shown to be the site of the comedo-like opening of the cyst.

The accompanying photomicrographs show well the unusual microscopic appearance of this tumor. The comedo-like opening is seen to connect directly with the cyst, which is filled with layers of horny substance and numerous lanugo hairs. At various places from the cyst wall diverticula, containing horny material and coiled-up hairs, extend out like pockets, into which open one or more hair follicles.

The epithelium of the cyst wall is similar in most respects to the epidermis of the skin with which it is continuous. The pigment, however, of the rete cells of the epidermis extends only through the comedo-like opening and is not present in the epithelium of the cyst wall proper. The granular layer of the epidermis, however, is found in a most modified form throughout the epithelium of the cyst wall. Papillæ, such as occur in the true skin, are absent.

The most striking feature presented by the cyst is the large number of modified hair follicles which spring from all parts of its wall. The hair follicles begin as short, thick pedicles, which very quickly branch into short finger-like processes, many of which contain lanugo hairs. It can be very definitely shown, either in a single section or by serial sections that these hair-containing follicles branch, and that at times two or more hairs are contained in a single follicle. Springing from these hair follicles and at times directly from the cyst wall are other finger-like processes which do not contain hair, nor have they a lumen, although their cellular elements resemble in every way the cells of the hair-containing follicles. It is a question if these processes represent developing hair follicles or rudimentary sebaceous glands. No definite sebaceous glands are present.

General Considerations.

It seems to be far from proven that a congenital tumor, formed by the snaring-off process, can be connected with the surface by an opening such as occurs in this case. Török,[1] in

FIG. 1.—Vertical section through cyst showing opening to the surface and groups of branching hair follicles growing from its walls.

FIG. 3.—Diverticulum in the walls of the cyst filled with hair and horny material and from which branch out a number of hair follicles.

FIG. 2.—Section showing an enlarged branching follicle containing multiple hairs

1891, reported such cases, but Unna [2] considered them "doubtful specimens." These cases showed some hair and sebaceous glands, both of which might occur in ordinary retention cysts. Török considered them as instances of congenital cysts, chiefly on account of their location, contents and the presence in their walls of ordinary skin papillæ. These criteria are of value when taken with other evidence, but by themselves are not conclusive (Unna [2]).

In the cyst here described we have a highly specialized structure, namely, the hair follicle, of which the anlage, at least, must have been present at birth. As hair follicles normally occur only in the skin, therefore, at least a sufficient portion of epithelium, containing a number of anlages of hair follicles corresponding to the groups of hair follicles in the cyst, must have been invaginated from the surface during fœtal life. Such specialized structures could develop from a cyst in no other way. Although hair follicles are prone to develop epithelial buds, it is inconceivable that such buds should develop during middle life into specialized structures such as hair follicles.

One must, therefore, come to the conclusion that this is definitely a congenital cyst of the dermoid type. Why the opening has remained is difficult to explain. The simplest and most probable explanation is that the lanugo hair, which appeared several months before the tumor, forced its way up through the surface epithelium as a result of the activity and growth which commenced at that time. This explanation is strengthened by the appearance in the scar, some time after the operation, of a lanugo hair, the follicle of which, as serial sections showed, was a lateral branch of the cyst which had not been entirely removed and, continuing to grow, had forced its way through the surface epithelium. If this hair could thus penetrate to the surface after the operation, there is no reason to question its ability to do so before the cyst was removed. This would have been the more easy to do if the fœtal invagination had been incomplete and a pedicle of epithelial cells had remained connecting the snared-off portion with the surface. In the healing of wounds, in which the upper portions of hair follicles have been destroyed, the continued growth and development of the follicle can take place [3].

A study of the sections shows that the different hair follicles are in all stages of development, which suggests that only the embryonic fundaments, or, at most, very early stages, of all or most of the follicles, were present when the tumor began to grow four years ago. At this time the follicles began to develop and enlarge and, as a result of this activity, there was formed the horny material and the hair which go to make up the tumor mass.

CONCLUSIONS.

The tumor, then, was a congenital or dermoid cyst showing definitely a comedo-like opening to the surface of the skin, remarkable because of the numerous groups of hair follicles branching out from the cyst wall. Its germ or anlage no doubt consisted in a simple epithelial invagination, enclosing a number of anlages of hair follicles, which were formed during early fœtal life, either before or after the hair follicles had begun to develop. In either case the further development was probably arrested after this invagination had taken place and was resumed only in adult life at the time the tumor formed.

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2. Unna: Histopathology of the Diseases of the Skin, pp. 1158-1163.
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THE MECHANISM OF LABOR IN SPONTANEOUS EVOLUTION.

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From time immemorial it has been recognized that neglected transverse presentations are associated with an excessive maternal and fœtal mortality and this belief became accentuated after the researches of Bandl and his successors had made us familiar with the physiology of the lower uterine segment and the mechanism of rupture of the uterus. Consequently, all modern obstetricians teach that for practical purposes transverse presentations are not susceptible of spontaneous delivery and urgently demand operative interference. This consists in version and extraction of the fœtus, if the patient is seen before the uterus has contracted tightly down upon its contents; or in decapitation, if the shoulder has become so firmly impacted in the pelvis that version is either impossible or promises to be attended by such risk of traumatic rupture of the uterus that an attempt to effect it is not justifiable.

This being the case, competent obstetricians no longer feel justified in pursuing an expectant course in the presence of this abnormality; consequently, they have an opportunity of seeing what nature may occasionally accomplish only when patients come into their hands after having been neglected by ill-trained physicians or midwives.

At the same time it is well known that spontaneous labor may occasionally occur in transverse presentations under conditions which ordinarily would appear to be desperate. Such an outcome may be effected in one of three ways: spontaneous version, *partus conduplicato corpore,* or spontaneous evolution. The first eventuality, which was described by Bartholin in the 17th century, usually occurs in the first stage of labor before the cervix has become fully dilated and usually before rupture of the membranes. It results in the gradual rotation of the child about its long axis in such a manner as to bring

either the head or the breech into relation with the superior strait. In this event the child is born by the head or by the breech by the usual mechanism, and there is nothing about the subsequent history of the labor to indicate the seriousness of the original situation.

Partus conduplicato corpore, or birth with the doubled body, was first accurately described by Roederer in 1756. Since then it has been frequently observed, and is generally admitted to be possible whenever pregnancy is terminated at a period when the fœtus is sufficiently small to permit both its abdomen and thorax to pass through the pelvis at the same time. Consequently the mechanism is usually observed during the premature birth of a macerated fœtus.

Spontaneous evolution, on the other hand, may occur when the child is well developed, and is a complicated process in which birth is effected with the shoulder remaining the presenting part. Such an outcome was described by Denman in 1772 and by Douglas in 1811, and requires an elaborate mechanism, which is possible only under exceptional circumstances. Following the first observations of Denman, numerous examples of spontaneous evolution have been described, but even at the present time the statements of authoritative writers as to the details of the process do not correspond and a great deal of confusion still exists.

In this paper I shall describe two cases of spontaneous evolution which occurred during my service as resident obstetrician at The Johns Hopkins Hospital, and afterwards I shall consider some of the disputed points in connection with the process. I am obliged to confess, however, that it will not be possible for me to solve the problem in a thoroughly satisfactory manner.

Case I.—*Spontaneous Evolution from R. Ac. D. A.* S. S., House No. 5108, October 24, 1911; 27 years old, Russian, married four years. Has had four spontaneous labors, and is uncertain as to the date of the last menstrual period. Pelvis normal; measurements 26, 28, 30, 21.5 cm., D. C. 11.75 cm.; arch fair, tubers. 9.75 cm.

The patient was first seen by the out-patient obstetrician at 10 p. m., when the following history was obtained: Pains began at 3 p. m. Soon afterwards the membranes ruptured spontaneously and a *fœtus compressus*, 16 cm. long, was passed. After this the pains were strong and frequent, and at about 7 p. m. the midwife found a hand in the vagina. She called a physician, who confirmed her diagnosis of transverse presentation and sent to the hospital for assistance.

When seen by us, the patient was having severe pains at two-minute intervals. General condition good. External examination was unsatisfactory, owing to almost tetanic contraction of the uterus. Fœtal heart not heard. On separation of the labia a hand was visible, but it was too high up to be identified; a few minutes later it came into view and proved to be the left hand. Rectal examination showed that the head was in the right flank, the left shoulder impacted in the pelvis, breech on the left side and back anterior—R. Ac. D. A. As the shoulder could not be lifted out of the pelvis and the uterus was almost tetanically contracted, it was determined to admit the patient to the hospital.

She was given morphin gr. ¼ hypodermically before the arrival of the ambulance at 10.30 p. m. During the trip to the hospital the pains were very severe, and upon arriving at the front door the patient stated that she thought the child was being born. She was accordingly rushed to the examining room, when examination showed that the left arm and shoulder and both buttocks were protruding from the vulva, the latter occupying its posterior part. Immediately afterwards the breech descended in the frank position and was followed by both legs and feet, which came down behind the left arm and shoulder, the right arm and shoulder being still within the birth canal. These were rapidly extruded, the head being born last. The placenta followed spontaneously within a few minutes.

The child was dead and unusually limp, but showed no signs of maceration. It weighed 2690 gm., was 50 cm. long and presented the following head measurements: 12.5, 11.5, 10.8, 8.75 and 7 cm. The left arm was swollen and purplish in color, while an oval area 8 x 12 cm., with the left shoulder as a center, presented a similar discoloration, and was in marked contrast to the rest of the surface of the child. This represented the portion which had first become engaged and later had protruded from the vulva.

The child was then taken to the laboratory and it was found that its neck was unusually long and pliable. When placed in a normal pelvis it could be forced through it by exactly the same mechanism as had been observed at the time of labor, thus affording positive evidence that the child had been born by spontaneous evolution by Douglas' mechanism. Numerous photographs were taken, from which the accompanying pictures were drawn.

At the time of admission the patient had a temperature of 100.4° F. and a pulse of 100. Both remained more or less elevated for the first 13 days of the puerperium, the highest temperature being 102° and the highest pulse 120. On the afternoon of the fifth day without any warning, the patient had a hæmorrhage. When seen a few minutes later she had lost about 500 cc. of blood. The fundus was large and boggy and reached to the level of the umbilicus. Massage and ergot by the mouth failed to control the bleeding. On internal examination the cervix was found to be patulous and the finger introduced through it detected a small tag of placental tissue adherent to the anterior wall and fundus. Upon removal it was found to measure 2 x 2.5 cm. The uterus then contracted well, and the bleeding ceased—the total amount of blood lost being approximately 700 cc.

The patient was discharged on the 17th day in good condition with the following findings: Outlet moderately relaxed; cervix, slight tear on left side; uterus forwards, movable, well involuted; slight thickening of the left broad ligament.

Case II.—*Spontaneous Evolution from L. Ac. D. P.* N. J., House No. 6736. July 27, 1914. A 26-year-old colored woman, who had had a spontaneous labor four years before. Last menstrual period December, 1913. Pelvis generally contracted; measurements 24, 27, 30, 18, 9.5 cm. Pubic arch narrow; tubers. 8.5 cm.

The patient was registered in the out-patient department (No. 6514) but when labor began, sent for a colored physician, who later called another physician in consultation. After repeated examinations a diagnosis of shoulder presentation was made, and it was requested that the patient be admitted to the hospital.

She was seen by the out-patient obstetrician at 7.40 p. m., when it was learned that labor had begun at 5 p. m. of the previous day and that the membranes had ruptured about 4.30 p. m. this afternoon (July 27). The patient was in bed, very restless and had a temperature of 102.4° F. Palpation showed the fundus four fingers below the xiphoid, the uterus tetanically contracted with the contraction ring running horizontally just about the symphysis. Several subserous myomatous nodules were palpable, and the round ligaments were parallel, but not greatly hypertrophied. Palpation was unsatisfactory, but the fourth maneuver showed that the presenting part was soft and compressible. The fœtal heart was not heard, but the mother stated that she had felt distinct movements during the morning.

The pains were of great intensity and occurred every three

minutes, with scarcely any interval between them. The left arm was protruding from the vulva, with the palmar surface of the hand directed upward and toward the right thigh of the patient. When the vulva was spread apart, the left axilla and a portion of the thorax could be seen. Rectal examination showed that the pelvis was filled with the body of the child, whose back was directed to the left and posteriorly. Consequently, a diagnosis of left acromio-dorso-posterior position was made. There was no bulging of the perineum and the patient was given a quarter of a grain of morphin by the mouth and prepared for transportation to the hospital.

At 8.10 p. m. the vulva gaped and the perineum bulged distinctly. As spontaneous evolution was evidently in progress, it was felt advisable to defer the transfer of the patient until later. The arm and shoulder continued to advance and ten minutes later the back of the child came into view and was born sharply bent upon itself until the buttocks reached the perineum. The back of the child having been raised, the buttocks and legs escaped. Slight traction downward brought the occiput under the symphysis, and the head was readily delivered by elevating the body of the child. The right hand was born in extension along the side of the head. The placenta was expelled spontaneously immediately afterwards. There was practically no bleeding during or after the third stage, but two drams of ergotol were given by the mouth prophylactically. Except for the elevated temperature, the patient was left in good condition.

The child was dead, but not macerated. Owing to an unfortunate misunderstanding its body was not sent to the hospital. It weighed 2500 gm. and was 45 cm. long. Its neck was markedly elongated on the left side, and on stretching the arm the distance between the mastoid and the acromion was found to measure nearly 9 cm. The arm was swollen and bluish in appearance and with the scapula formed the center of a "caput succedaneum" 1 to 2 cm. thick. This was bluish and œdematous and involved an area, roughly speaking, 6 cm. in diameter, extending from the left breast to the mid-back, and from the left side of the neck midway to the iliac crests.

Following delivery the patient continued to have fever and an elevated pulse, more or less abdominal pain, and difficulty on micturition. A diagnosis of pyelo-nephritis and localized pelvic peritonitis was made and she was admitted to the hospital on the 12th day after delivery. At that time the following findings were noted: Outlet somewhat relaxed; no sign of fistula; cervix almost flush with vaginal vault, deep bilateral laceration; uterus forwards, slightly enlarged, drawn somewhat to the left side and firmly fixed; adnexa not felt, but on both sides there was an area of induration involving the fornix and posterior vaginal wall which appeared to constrict the rectum. The urine contained a considerable quantity of albumin, some red cells and leucocytes, epithelial cells and a few granular casts. Wassermann negative.

The patient gradually improved on conservative treatment and left the hospital in good condition.

These two cases are of interest for several reasons. Firstly, on account of their rarity, as they are the only examples of birth by spontaneous evolution observed in 13,000 consecutive labors in the Obstetrical Department of The Johns Hopkins Hospital. Secondly, they show that the final stages of the process may be completed with great rapidity, the first child having been born practically in the ambulance, while the second was expelled so rapidly that the patient could not be transported to the hospital. Furthermore, the first case shows that the entire duration of labor may be relatively short, being only eight hours.

Finally, the first case is of particular interest from the fact that it was possible in the laboratory to force the child through a normal pelvis by a mechanism identical with that observed at the bedside, and to photograph its various stages. From these photographs Mr. Max Broedel was kind enough to prepare the drawings which accompany the article, and which graphically illustrate the main steps in the mechanism.

Fig. 1, which shows the first stage of spontaneous evolution —namely, the impaction of the shoulder into the pelvis, together with the molding and transverse compression of the fœtus—does not belong in this series; but is nevertheless strictly accurate, as it was drawn from a fœtus contained in a uterus which had been removed at full term on account of atresia of the cervix and profound intra-partum infection, the child being already dead. The entire specimen was hardened in formalin, after a window had been cut in the uterine wall, and was not opened for some weeks, so that the postural relations were accurately preserved.

Fig. 2 shows the condition of affairs after the arm had prolapsed through the vulva. Note the molding of the entire fœtus, the attitude of the head, the elongation of the neck, and the swelling and discoloration of the prolapsed arm. This last condition seems to afford indubitable evidence that fœtal death had occurred comparatively late in labor and after the arm had prolapsed.

Fig. 3 is of unusual interest, as it represents the crucial stage in the mechanism, and shows conditions which are particularly difficult to explain. In the first place, note that the occiput has rotated almost directly anteriorly and lies just above the right horizontal ramus of the pubis and the symphysis; while the neck is in contact with the inner surface of the symphysis, and has become so stretched and elongated as to permit the left shoulder to emerge beneath the pubic arch. At the same time the buttocks are seen to have emerged from the outlet with their anterior surface in contact with the inner surface of the prolapsed arm. The position of the buttocks is very unusual, is particularly difficult of explanation, and seriously complicates the classification of the mechanism, as will be indicated later. It can be explained only by assuming that, after the left shoulder had emerged beneath the pubic arch, the buttocks had been forced down between the thorax and the posterior pelvic wall, so that they eventually emerged behind the prolapsed arm. It is apparent that such a maneuver must have necessitated great compression and an extreme degree of torsion of the body, which could scarcely be compatible with the life of the child. Consequently, it is permissible to assume that fœtal death must inevitably have taken place at that time, if it had not occurred previously.

Fig. 4 shows that after delivery of the shoulder and buttocks the child had undergone a movement of rotation, by which the prolapsed arm returned to the side of the mother toward which it was originally directed, thus bringing the occiput under the pubic arch in the most suitable position for easy expulsion.

In the second case the evolution was clearly effected by the mechanism described by Douglas, but it is not so easy to explain which mechanism was concerned in the first case.

Before attempting to do so, I shall refer to the histological aspects of the subject, as only in that way will it be possible to find one's way among the contradictory statements which have been made concerning the mechanisms of Denman and Douglas and the relative frequency with which they occur.

As has already been indicated, the term spontaneous evolution was introduced by Sir Thomas Denman in the latter part of the 18th century, and the first reference to it which I have been able to find is in an article in the London Medical Journal for 1785, entitled "Observations to prove that in cases where the upper extremities present, at the time of birth, the delivery may be effected by the spontaneous evolution of the child." In this article Denman reported three personal cases, and stated that including these some thirty cases had been observed. I shall quote his first case verbatim:

CASE I.—In the year 1772 I was called to a poor woman in Oxford street, who had been in labor all the preceding night, under the care of a midwife. Mr. Kingston, now living in Charlotte street, and Mr. Goodwin, surgeon at Wirksworth, in Derbyshire, who were at that time students in midwifery, had been sent for some hours before I was called. The arm of the child presenting, they attempted to turn and extract it by the feet, but the pains were so strong as to prevent the introduction of the hand into the uterus. I found the arm much swelled and pushed through the external parts in such a manner that the shoulders nearly reached the perineum. The woman struggled vehemently with her pains, and during their continuance I perceived the shoulder of the child to descend. Concluding that the child was small and would pass doubled, through the pelvis, I desired one of the gentlemen to sit down to receive it, but the friends of the woman would not permit me to move. I remained by the bedside till the child was expelled, and I was very much surprised to find that the breech and inferior extremities were expelled before the head, as if the case had originally been a presentation of the inferior extremities. The child was dead, but the mother recovered as soon and as well as she should have done after the most natural labor.

The essentials of the other cases are contained in the following quotations: Case II: "No further attempts were made to turn the child. Then every pain propelled it lower into the pelvis, and in a little more than one hour the child was born, the breech being expelled as in the first case." Case III: "On examination the arm pushed through the external parts, the shoulder pressing firmly upon the perineum. The exertions of the mother were wonderfully strong. I sat down while she had two pains, by the latter of which the child was doubled and the breech expelled. I extracted the shoulders and head and left the child in bed." From these descriptions it is impossible to learn exactly what occurred, except that the children had been born spontaneously, and that the breech had been expelled before the head.

Moreover, it is apparent that Denman was not quite certain himself, as is clearly shown by the following statement at the end of the article:

Though knowledge of the fact has already been attended with advantages to many women in very deplorable circumstances, much remains to be done to complete the doctrine, not by reasoning upon the subject, but by careful attention to practice.

As far as I can ascertain his first attempt to describe the mechanism was in a letter written to Douglas just after the appearance in 1811 of the first edition of his pamphlet, "The Explanation of the Real Process of the Spontaneous Evolution of the Fœtus," from which the following quotation is taken:

As to the manner in which this evolution takes place, I presume that after the long continued action of the uterus, the body of the child is brought into such a compact state as to receive the full force of every returning action. The body in its doubled state, being too large to pass through the pelvis, and the uterus pressing upon its inferior extremities, which are the only parts capable of being moved, they are forced gradually lower, making room, as they are pressed down, for the reception of some other part into the cavity of the uterus which they have evacuated, until the body, turning as it were upon its own axis, the breech of the child is expelled, as in an original presentation of that part; nor has there been anything uncommon in the size and form of the pelvis of these women, to whom this case has happened, nor have the children been small or softened by putrefaction.

Douglas, in the second edition of his monograph which appeared in 1819, took issue with Denman, and stated that while spontaneous evolution undoubtedly occurred it was effected by an entirely different mechanism. This opinion was based upon his personal observation of seven cases, in all of which the arm and shoulder of the child emerged from the vulva before the rest of the body; and this being the case he contended that it was impossible for the breech to be born first. He described as follows the situation of the fœtus immediately prior to its expulsion:

The entire of it somewhat resembles the larger segment of a circle; the head rests on the pubis internally; the clavicle presses against the pubis externally, with the acromion stretching towards the mons veneris; the arm and shoulder are entirely protruded, with one side of the thorax not only appearing at the os externum (vulva), but partly without it; the lower part of the same side of the trunk presses on the perineum, with the breech either in the hollow of the sacrum or at the brim of the pelvis, ready to descend into it; and by a few uterine efforts the remainder of the trunk, with the lower extremities, is expelled. And to be still more minutely explanatory in this ultimate stage of the process, I have to state that the breech is not expelled sideways, as the upper part of the trunk had previously been; for during the presence of that pain, by which the evolution is completed, there is a twist made, about the center of the curve, at the lumbar vertebræ, when both buttocks, instead of the side of one of them, are thrown against the perineum, distending it very much; and immediately after the breech, with the lower extremities, issues forth, the upper and back part of it appearing first, as if the back of the child had originally formed the convex and its front the concave side of the curve.

So convincing was Douglas' exposition, that Walter Channing, in an appendix to his American edition of Denman's Aphorisms, stated that Denman's interpretation of the process was incorrect; and still further support was lent to this doctrine by the contributions of Dubois. This view obtained immediate acceptance among English and French writers, and Tarnier and Chautreuil, Ribemont-Dessaignes and Lepage, Puech and Lequeux, Rouvier and other French writers describe Douglas' mechanism as the only one obtaining in spontaneous evolution. Indeed, Puech and Lequeux state that Denman's mechanism does not occur, and that the cases which have been described as such are really examples of spontaneous evolution.

FIG. 1.

FIG. 3.

FIG. 2.

FIG. 4.

On the other hand, German authorities have clung to Denman's explanation, which was the only one mentioned by Küstner in Müller's Handbuch der Geburtshilfe. Von Franque and Zangemeister, who have recently written extensively upon the subject, hold that spontaneous evolution may be effected by either the Douglas or the Denman mechanism, but that the latter is comparatively infrequent. Thus, of 55 cases collected by Zangemeister, in which full details of the process were available, in only 12 was the delivery by Denman's mechanism; and several of these were doubtful.

Furthermore, when one studies the detailed description of the latter, as given by Zangemeister, it becomes apparent that it differs in many respects from the process described by Denman. According to Zangemeister, this mechanism usually occurs in dorso-posterior positions, and can be effected only by the buttocks being pushed past the impacted shoulder. As the buttocks descend, the shoulder gradually rises out of the pelvis and draws up the arm with it. At the same time, the head, instead of rotating anteriorly, moves posteriorly and eventually comes to lie over one of the sacro-iliac joints in front of the promontory. In this event the shoulder is not the first part of the child to emerge from the vulva, but rather the lower abdomen or the buttocks. After the breech has been expelled, the abdomen, thorax, shoulders and head successively emerge.

That almost fully developed children may be delivered by such a mechanism must be admitted, as it is vouched for by Zangemeister and other competent German authorities. But I contend that it is scarcely justifiable to describe it as Denman's mechanism. In the first place it does not correspond with Denman's theoretical explanation, which called for a rotation of the fœtus about its long axis, and in the second place, it does not tally with Denman's description of the course of labor in his Case I, in which he "perceived the shoulder of the child to descend." Furthermore, he did not claim that the breech was expelled before the anterior shoulder, but merely reported that "he was very much surprised to find that the breech and inferior extremities were expelled before the head." As this likewise happens when the child is born by the Douglas mechanism, it seems gratuitous to assume that it was expelled in any other way.

For these reasons it appears to me to be inexpedient to continue to speak of a Denman mechanism, more particularly as careful study of a number of the reported cases makes it quite possible that the respective authors were mistaken as to what had actually occurred.

Reverting once more to my first case, it seems to me to be unjustifiable to describe it as an example of spontaneous evolution by Denman's mechanism, for the reason that the arm and shoulder were born before the breech. Consequently, it would appear best to classify it as an instance of an abnormal or complicated Douglas' mechanism.

I am perfectly conscious that what I have put forward has contributed but little to our knowledge, but if it leads to increased interest in the subject of spontaneous evolution, I shall feel amply repaid for my trouble in preparing this article.

In conclusion, I desire to express my thanks to my former chief, Dr. J. Whitridge Williams, for permission to publish the cases, and for many suggestions in the preparation of this article.

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NOTES ON NEW BOOKS.

The Brain in Health and Disease: By JOSEPH SHAW BOLTON, M. D., D. Sc., F. R. C. P. (Lond.). (*New York: Longmans, Green & Co.*)

In the introduction the reader is warned that the work must not in any sense be considered a text-book on mental disease, but that it should rather be looked upon as in the nature of a treatise on general cerebral physiology and pathology. The work is really based on original researches of the author carried on during the past eighteen years, and it gives ample proof of laborious, painstaking, and in some ways very interesting efforts. It is divided into two parts dealing with cerebral function in the normal and in the insane brain, respectively. The latter portion is subdivided into sections dealing with cerebral function in the sub-normal or sub-evoluted brain (amentia), and in the involuted or dissoluted brain (dementia). Under these two headings of Amentia and Dementia all mental diseases are classified.

In considering the general histology of the cerebral cortex the author's method of micrometric measurement of the primary cell and fiber-laminæ is fully described and it is very interesting, but he gets quite out of his depth when he attempts to draw clinical correlations. His method of examination consists in measuring accurately vertical sections from four regions of the convolutions, and then from these a general average measurement is obtained. The regions recommended are the *flat surfaces* or external parts

between fissure lips, the *apices* or fissure lips, the *bottoms* of fissures, and the *sides* of fissures at some point between the apices or fissure lips and the bottom of the fissures. This method of examination is no doubt a very ingenious one, but after his results have all been recorded and summarized, the following final remark is added: "I would add that there is reason to believe that this physical basis of the cerebral functions, which exhibits such well-marked variations in the subjects of mental alienation, exhibits equally important though less extensive variations in the case of presumably normal individuals."

In reference to the above remark it must be noted that no guides are given so as to enable one to say when the normal ceases and when the abnormal begins. Furthermore, when one finds such conditions as hysteria, paranoia, and recurrent insanity classified as states of sub-evolution or amentia, one is inclined to question the author's clinical experience. If he had confined himself to a description of the histo-pathology of the cerebral cortex, and had not attempted to draw clinical deductions, it would have been a pleasure to congratulate him on his work, but his clinical observations are so confused and so little analyzed that for students the book would be most misleading. D. K. H.

Pharmacology, Clinical and Experimental. By HANS H. MEYER and R. GOTTLIEB. Authorized English translation by JOHN TAYLOR HALSEY. Price, $6.00. (*Philadelphia: J. B. Lippincott Company, 1914.*)

This book is the result of years of work and thought along the lines of pharmacology on the part of two leading European pharmacologists. It can be read with profit by every up-to-date scientific man of medicine. It has a peculiar value for the teacher of medicine.

Whereas most books on the subject begin with a consideration of drugs, this one starts each chapter with a description of an organ or system of organs together with functional considerations and the mechanism normally involved. The reader is thus oriented anatomically and physiologically. The influence of each drug concerned is then brought into relation in such a way that the reader obtains an unusually clear picture of its pharmacological action. This arrangement of material is excellent. Diagrams enhance the value of the work.

The translation is good and Dr. Halsey has added many valuable remarks and suggestions. L. G. R.

Nervous and Mental Diseases. By ARCHIBALD CHURCH, M. D., Professor of Nervous and Mental Diseases in Northwestern University Medical School, Chicago; and FREDERICK PETERSON, M. D., formerly Professor of Psychiatry, Columbia University. Eighth edition, revised. Octavo volume of 940 pages, with 350 illustrations. Cloth, $5.00 net; half Morocco, $6.50 net. (*Philadelphia and London: W. B. Saunders Company, 1914.*)

In the eighth edition the section devoted to nervous diseases has been modified here and there, but on the whole there is comparatively little change in the material. In the preface reference is made to the changes introduced in the paragraphs dealing with syphilis of the nervous system and with investigations of the cerebro-spinal fluid. As a matter of fact no reference is made to Lange's colloidal gold test, and the whole subject is discussed in a very formal and somewhat inadequate manner.

The section on mental diseases does not attempt to discuss broad psychiatric issues, but consists of a rather formal classification of the psychoses with a detailed description of well-known text-book entities.

The book is not calculated to stimulate the interest of the medical student in mental diseases. C. M. C.

Burdett's Hospitals and Charities. 1915. Being the Year Book of Philanthropy and the Hospital Annual. By SIR HENRY BURDETT, K. C. B., K. C. V. O. Twenty-sixth year. (*London: The Scientific Press, Limited, 1915.*)

The above volume has made its appearance with commendable punctuality notwithstanding the delay which might have been expected in consequence of the unsettled state of affairs in Europe.

The book itself contains the usual information which has been so valuable to all hospital administrators during the past 25 years. The only feature of value before us which requires special mention is a new chapter on the "Future Outlook and the Extension of Voluntary Hospitals." This is an interesting chapter because it contains a plea for bringing the voluntary hospitals, or as we would say in this country the corporate hospitals, of England more into accord with the methods which exist in the United States. It is evident that the editor, Sir Henry Burdett, is a man of strong political bias, as shown by his arraignment again and again of the politicians who procured the passage of the National Insurance Act. He charges that they do great damage to voluntary hospitals by ignoring the fact that insured persons when seriously ill require hospital treatment; and consequently making no provision for it. He believes that this has brought a severe burden upon the managers of these hospitals, which have been crowded by insured persons to the exclusion of the industrial class, who are not insured. He declares that if the example of Germany and other foreign countries had been followed, where adequate hospital treatment for insured persons is supplied in connection with such insurance, at least 50,000 additional beds ought to have been provided in the hospitals of the United Kingdom. But nothing has been done.

It is also asserted that at the present time all voluntary hospitals have a twofold demand made upon them, arising out of the necessity to care for wounded soldiers, and to carry out the provisions of the National Insurance Act, both of which tend to crowd them to the exclusion of indigent persons for whom the hospitals were originally created.

In the opinion of the accomplished editor the only remedy to prevent a deficiency in funds for the support of voluntary hospitals is to be found in the reception and treatment of paying cases who are able to make an adequate compensation for their care and treatment, and also for persons in less comfortable circumstances who are not insured but who are able to pay some portion of the cost of treatment. He cites the example of the United States to show how much can be done to help voluntary hospitals in this way.

He states very forcibly that voluntary hospitals have a strong hold upon the minds of the well-to-do class, who appreciate their efficiency and what they have done for medical science, and who are looking for opportunities for personal service. In his judgment they are a valuable asset to the community and should be fostered in every way.

Under the chapter entitled "British Hospital Progress" he notes the tendency to establish in connection with general hospitals separate wards for the treatment of venereal diseases, and believes that the effect has been to lessen the amount of suffering from them, and to safeguard the community.

The loss of surgical attendants and members of the nursing staff in voluntary hospitals in consequence of the war is deplored, and fears are expressed that it may be difficult to ask from the hospitals the proper care of sick and wounded soldiers, and at the same time secure care and treatment of the sick poor from them.

The tribute to the voluntary hospital on page 102 is worthy of being cited here:

"The voluntary hospital from the moment it became a great center of education—scientific, technical, moral, mechanical, and

personal—has as a necessary consequence increased yearly in value as a storehouse and center of knowledge. Who can estimate, nay, who can exaggerate, the value to the race and to humanity everywhere of the knowledge gathered up by experience and practised in a great modern hospital for the sick? All this knowledge and every addition made to it is transmitted through able teachers—some of the greatest and most proficient scientists and the most devoted and skilled members of the nursing profession—to those who, when equipped with knowledge and depth in the practice of their profession by the skill they have acquired in the hospital, go forth into the world to carry on the beneficent work amongst all who may fall out on life's journey when struck down by sickness or overtaken by accident. To-day the knowledge garnered and preserved in the hospital storehouse is systematized and reduced to order upon a carefully thought-out plan, which makes it readily available for use at all times, not only by members of the present generation, but for those who are to follow."

A marked feature of the book is the insistent demand which he makes that the Government shall come to the assistance of these hospitals by freeing them from taxation, by providing duty-free alcohol, and by calling upon all philanthropists to assist them.

The volume contains its former valuable statistics.

It is to be hoped that the time will come when a similar publication can find a field in the United States.

During the 26 years of publication this annual has done much to unify hospital methods and to increase interest in hospitals throughout the world. H. M. H.

Biochemic Drug Assay Methods. With Special Reference to the Pharmacodynamic Standardization of Drugs. By PAUL S. PITTENGER, PH. G., PH. C., PHAR. D. Edited by F. E. STEWART, M. D., PH. G. Cloth, $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1914.*)

This small volume of 140 pages describes in considerable detail the most frequently used methods of biochemically standardizing drugs. It is elementary in character, well illustrated and gives the formulæ of various solutions employed. It deals with the standardization of cardiac stimulants and depressants, epinephrin and products of the suprarenal glands, ergot, pituitary extract and cannabis indica. A fairly complete bibliography is attached.

Attention might be called to a typographical error. Locke's solution is referred to as Loche's solution. The book will prove of decided value to pharmacologists and therapeutists.

L. G. R.

Modern Medicine: Its Theory and Practice. Edited by SIR WILLIAM OSLER, BART., M. D., F. R. S., and THOMAS MCCRAE, M. D. Second edition. Vol. II. Diseases caused by Protozoa and Animal Parasites; Diseases due to Physical, Chemical and Organic Agents; Diseases of Metabolism and of the Respiratory System. (*Philadelphia: Lea & Febiger, 1914.*)

The titles covered by this volume indicate its importance. The general field of protozoology has been included in medicine, in which so much change is taking place.

The names of Richard Strong, Charles Craig Stephens, Sir David Bruce, John Todd, are a guarantee that the articles are up to date and authoritative.

Part II contains Dr. Stiles' brief résumé of human (metazoan) parasites, which is the only publication of the kind in the English language that is reasonably complete. This section alone is worth the price of the volume.

It is interesting to note the change in the notice given pellagra in the two editions. In the first edition (1907) it was accorded a paragraph of ten lines under food poisons. The new edition contains an admirable article by Beall, consisting of 17 pages with two good plates.

Altogether, the second volume is fulfilling admirably the promise of improvement in format, page, illustration and binding, and the subject-matter is hard to equal in any system.

T. R. B.

Pathogenic Microörganisms. By WILLIAM HALLOCK PARK, M. D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City; and ANNA W. WILLIAMS, M. D., Assistant Director of the Bureau of Laboratories, Consulting Pathologist to the New York Infirmary for Women and Children. Fifth edition. Cloth, $4.00. (*Philadelphia: Lea & Febiger, 1914.*)

This book has undergone a most interesting evolution. The first edition, called "Bacteriology of Medicine and Surgery," published by Park, was intended almost entirely for medical practitioners. The subsequent editions have been gradually made more comprehensive until the present, which must rank not only as a most valuable reference work for the use of physicians but also as one of the best text-books of bacteriology for the student's use.

In the present edition there is an advantageous rearrangement of the subject-matter, a thorough revision of many of the chapters and a new chapter on filtrable viruses. But most important is the fact that all of the very latest work has been judiciously criticised and incorporated in the text. The illustrations are splendid; the bibliography, although incomplete, will prove of material assistance to the reader. In fine, it may be said that the value of the book for physicians, students and laboratory workers is permanently established. M. C. W.

Pyelography. By WILLIAM F. BRAASCH, M. D. Cloth, $5.00. (*Philadelphia: W. B. Saunders Company, 1915.*)

The author is to be congratulated upon the very valuable work which he has presented to the medical profession. With the wealth of material at his command, he has been able to cover the subject from every conceivable standpoint.

His subject has been treated exclusively from an X-ray standpoint, and what can be deduced from this method of examination. It has been treated systematically, and practically every variation of the renal pelvis, whether anatomical of pathological, has been taken up.

It is very difficult indeed to pick out any distinctive chapter, as the subject-matter throughout is so good that no one part stands out more than the other. Mention, however, must be made of the chapter on the normal pelvis. All the variations that are to be found in a normal pelvis have been taken up. Each has been so thoroughly described and illustrated that one gets an absolutely clear conception of the subject. To anyone who is familiar with this type of work, the value of these illustrations is apparent at once, as so frequently the question arises as to whether we are dealing with a variation of a normal pelvis or the beginning of a pathological condition.

Then, too, his chapter on technique is to be especially commended, as it describes so thoroughly the proper method for making this examination. The importance of this point can hardly be insisted upon too strongly, in view of the fact that in the hands of a beginner the injection of the pelvis of the kidney is sometimes done in a careless and haphazard manner, which not only fails to give results, but also is actually dangerous to the patient.

After the chapter on technique and the normal pelvis, Braasch takes up successively the abnormal positions of the kidneys, the mechanical dilatations, the inflammatory dilatations, calculi, renal tumors and congenital anomalies. Each subdivision, however, is described and illustrated.

In conclusion, it may be said that the book is of great value from two standpoints: first, it contains a very excellent description of the various conditions; and secondly, it presents a great number of very excellent illustrations, which puts it almost in the class of an atlas. F. H. B.

Radiography, X-Ray Therapeutics and Radium Therapy. By ROBERT KNOX, M. D. Cloth, $8.00 (*New York: Macmillan Company, 1915.*)

In the preface the author states that the object of this work is to present to the student and practitioner, in as concise and practical form as possible, the essential points in radiography, X-ray therapeutics and radium therapy. Reading the book from this standpoint, one can say that he has fulfilled his obligations.

It is perfectly true that in radiology one must have quite an understanding of the mechanics for the production of radiograms. Unfortunately, in the section of the book treating of radiology alone, a third of it is given up to the description of apparatus. Another third is devoted to the method of examination. The remaining third is made up largely of illustrations, with the briefest kind of description of the pathological conditions. This is rather unfortunate, as by far the most difficult thing in radiology is the interpretation of the radiograms. The mechanical part is easily mastered and, in fact, can be done by a skilled technician, but the real value of radiology lies in the proper interpretation of the findings; and it certainly would seem that, if less space were devoted to the technical part and more to what might be termed the truly medical part, a text-book would be of much more value, not only to the beginner, but even to the skilled radiologist.

As an instance of the brevity with which the various subjects are treated, the gastro-intestinal tract, as regards not only the normal but also the pathological conditions, is dealt with in about twelve pages. The section on therapy is short, but quite good. The final section of the book is devoted to radium therapy, and includes a discussion of the physics and the application of radium. F. H. B.

Diagnostic and Therapeutic Technique. A manual of practical procedures employed in diagnosis and treatment. By ALBERT S. MORROW, M. D. Second edition. Cloth, $5.00. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

This volume, of over 800 pages, covers a wide range of diagnostic and therapeutic measures, and includes practically everything that a general practitioner of medicine would be justified in attempting without the help of a skilled surgeon or specialist. In fact several procedures are included, such as direct arterio-venous anastomosis, which would better have been reserved exclusively for men with special training and experience. Aside from the ordinary simpler procedures, considerable space is devoted to anesthesia, local and general; to cystoscopy, and ureteral catheterization; to the instrumental treatment of strictures; to the simpler methods of examining the nose and sinuses, the pharynx, and larynx; and to the use of the bronchoscope and proctoscope.

In general the directions are brief, but clear and explicit, and are amplified by numerous illustrations. An attempt is made to indicate briefly the practical application of the methods outlined, and the dangers in, or contraindications to, their use.

As is inevitable, there are errors of omission, and statements to which exception may be taken. Thus, in discussing methods for the direct transfusion of blood, the use of syringes, the only method a man of ordinary training could hope to master, is discarded for the very difficult vessel-to-vessel method. Further, the outline of the dangers of agglutination or hæmolysis following the use of blood from unsuitable donors is very incomplete, and even misleading. The dangers of lumbar puncture, and particularly of intra-meningeal injections, where a syringe is used and the pressure exerted not accurately controlled, are not sufficiently emphasized.

On the whole, however, the book is a commendable one. It is not intended for the specialist, but should meet the demands of the student and general practitioner. P. W. C.

Medical Ethnology. By CHARLES E. WOODRUFF, A. M., M. D., Lieutenant-Colonel, U. S. Army Medical Corps (Retired). (*New York: Rebman Company, 1915.*)

The author explains in his preface that this work was begun as a revision of the first edition of his "Effects of Tropical Light on White Men," a book which some years ago attracted widespread and well-deserved attention, but that the title was changed to "Medical Ethnology" because of the development of our knowledge that many other factors besides pigmentation enter into the causation of the differences between the races and sub-races of men. It is a matter of congratulation to students of ethnology that this change of plan was made, as it has given the author an opportunity to present a mass of valuable data from his own experience in various parts of the world and the results of a wider study of the literature.

Medical ethnology may be briefly defined as the science which deals with the morbidity of races and the changes of types which result from their physical and mental reaction to their environment. Changes in type, the author asserts, are going on constantly, and the characteristics, tendencies and future of any given race cannot be explained or predicted without a full knowledge of its environment. Heredity is defined as an "organic inertia" of the individual or race and is in fact the inability of a person or species to modify itself to environment when placed among new surroundings. Such organic inertia explains also the reason why many races die out when transferred to unfavorable climates, or when called upon to meet conditions of life for which they are physically unfit. The type of the race sooner or later is produced by its environment.

The whole book is made up of the development of these ideas. It is full of interest, but unfortunately it does not lend itself to a brief summary and needs to be read from cover to cover. The effects of ether waves, infra-red and ultra-violet rays, X-rays and radium, are given in considerable detail to explain the effect of light upon growth and development. Unless races are able to adjust themselves to light and heat by protective pigmentation, they degenerate. Survival of migrants depends upon this and also upon physical characters such as the size and shape of the air passages and the openness of the nostrils. The effects of pigmentation, congenital or acquired, and the reaction of the nervous and physical systems to light should not be forgotten. Contrary to the opinion of medical men generally, the author believes that too much sunlight is injurious to all but the deeply pigmented races.

The chapters entitled "Causes of Extinction," "Ethnic Psychology" and "Practical Application of Medical Ethnology" are especially valuable. The book is the fruit of much thought and wide research.

The above imperfect and inadequate note had scarcely been written, when news came of the death of the accomplished author. All who knew him and were interested in his contributions to the science of race development and decay can but join in the heartfelt but unavailing regret that his life was not spared to complete his studies. It is evident that he had not reached final conclusions and was still gathering material for further deductions. A laborious and painstaking investigator like Colonel Woodruff is rare indeed in the ranks of the medical profession! H.

Principles of Hygiene. By D. H. BERGEY, A. M., M. D. Cloth, $3.00. (*Philadelphia: W. B. Saunders Company, 1915.*)

The fifth edition of Bergey's *Principles of Hygiene* deserves more than a word of commendation. The form and size of the earlier editions are retained, and to a large extent the clearness and simplicity which mark the presentation of the subject-matter. The general literature of hygiene has evidently been closely followed by the author, and this has made itself felt in certain chapters. Particularly should be mentioned the chapter on Food and Dieting, in which excellent tables illustrative of the caloric values of different articles of diet are to be found, and other tables giving an accurate comparison of caloric values and the cost of nearly all our foods. The subject of Industrial Hygiene is ably presented in a rather short chapter of less than 20 pages, and School Hygiene in a somewhat similarly brief but thorough manner. The sections on Military Hygiene and Naval Hygiene are of particular interest in the present world crisis. Finally, especial mention should be made of the chapter on Vital Causes of Disease, in which the important epidemiological factors relating to the ordinary infections are clearly brought out. W. W. F.

BOOKS RECEIVED.

Public Health Reports. Issued weekly by the United States Public Health Service. Containing Information of the Current Prevalence of Disease, the Occurrence of Epidemics, Sanitary Legislation, and Related Subjects. Vol. XXIX, Part I, Nos. 1-26, January-June, 1914. 1915. 8°. 1752 pages. Government Printing Office, Washington.

Southwestern Medical and Surgical Association. Transactions of the First Annual Session of the Southwestern Medical and Surgical Association. C. F. Braden, editor. 1914. 4°. 156 pages. El Paso, Texas.

The Gold-Headed Cane. By William Macmichael, M. D. With an Introduction by Sir William Osler, B. A., M. D., F. R. S. And a Preface by Francis R. Packard, M. D. 1915. 8°. 261 pages. Paul B. Hoeber, New York.

Radiography, X-Ray Therapeutics and Radium Therapy. By Robert Knox, M. D. (Edin.), M. R. C. S. (Eng.), L. R. C. P. (Lond.). With 64 plates, 246 illustrations in the text and a frontispiece in color. 1915. 4°. 406 pages. The Macmillan Company, New York.

A Reference Handbook of the Medical Sciences. Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. First and second editions edited by Albert H. Buck, M. D. Third edition, completely revised and rewritten. Edited by Thomas Lathrop Stedman, A. M., M. D. Complete in eight volumes. Vol. V. Illustrated by numerous chromolithographs and 733 half-tone and wood engravings. 1915. 923 pages. 4°. William Wood & Co., New York.

Pyelography (Pyelo-Ureterography). A Study of the Normal and Pathologic Anatomy of the Renal Pelvis and Ureter. By William F. Braasch, M. D. Containing 296 pyelograms. 1915. 8°. 323 pages. W. B. Saunders Company, Philadelphia and London.

Pathological Technique. Including Directions for the Performance of Autopsies and for Clinical Diagnosis by Laboratory Methods. By Frank Burr Mallory, A. M., M. D., and James Homer Wright, A. M., M. D., S. D. Sixth edition, revised and enlarged. With 174 illustrations. 1915. 8°. 536 pages. W. B. Saunders Company, Philadelphia and London.

The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Vol. IV, No. 2, April, 1915. 1915. 8°. W. B. Saunders Company, Philadelphia and London.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Vol. II. Twenty-fifth series. 1915. 8°. 312 pages. J. B. Lippincott Company, Philadelphia and London.

Medical Ethnology. By Chas. E. Woodruff, A. M., M. D. 1915. 8°. 321 pages. Rebman Company, New York.

Medical Applied Anatomy. For Students and Practitioners. By T. B. Johnston, M. B., Ch. B. Containing three full-page plates in color and 146 other illustrations in the text. 1915. 12°. 436 pages. A. and C. Black, Limited, London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Vol. II, June, 1915. 1915. 8°. 445 pages. Lea & Febiger, Philadelphia and New York.

Human Physiology. By Professor Luigi Luciani. Translated by Frances A. Welby. Vol. I. Circulation and Respiration. 1911. 8°. 592 pages. Vol. II. Internal Secretion; Digestion; Excretion; The Skin. 1913. 8°. 558 pages. Vol. III. Muscular and Nervous Systems. 1915. 8°. 667 pages. Macmillan & Co., Limited, London.

Stanford University Medical Publications. Bulletin No. 2, 1913-14. 4°. San Francisco, Cal.

What Every Mother Should Know about Her Infants and Young Children. By Charles Gilmore Kerley, M. D. 1915. 12°. 107 pages. Paul B. Hoeber, New York.

The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Vol. IV, No. 1, February, 1915. 1915. 8°. W. B. Saunders Company, Philadelphia and London.

The Vicious Circles of Neurasthenia and Their Treatment. By Jamieson B. Hurry, M. A., M. D. (Cantab.). With illustrations. 1915. 8°. 90 pages. J. & A. Churchill, London; P. Blakiston's Son & Co., Philadelphia.

University of Pennsylvania. Eighth Report of the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis. Factors Affecting the Health of Garment Makers. By H. R. M. Landis, M. D., and Janice S. Reed. 1915. 4°. 104 pages. Henry Phipps Institute, Philadelphia.

American Association for Study and Prevention of Infant Mortality. Transactions of the Fifth Annual Meeting, Boston, Mass., November 12-14, 1914. 1915. 8°. 391 pages. Franklin Printing Company, Baltimore.

University of Michigan. Contributions from the Department of Obstetrics and Gynecology. Vol. III, 1912-1914. 1914. 8°. Ann Arbor, Michigan.

College of Physicians. Transactions of the College of Physicians of Philadelphia. Third Series. Vol. XXXVI. 1914. 8°. 388 pages. Philadelphia.

John Shaw Billings. A Memoir. By Fielding H. Garrison, M. D. Illustrated. 1915. 8°. 432 pages. G. P. Putnam's Sons, New York and London.

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